Intra-tumoral TLR-9 activation
Can we Prime ?

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THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Presenter Disclosure Information

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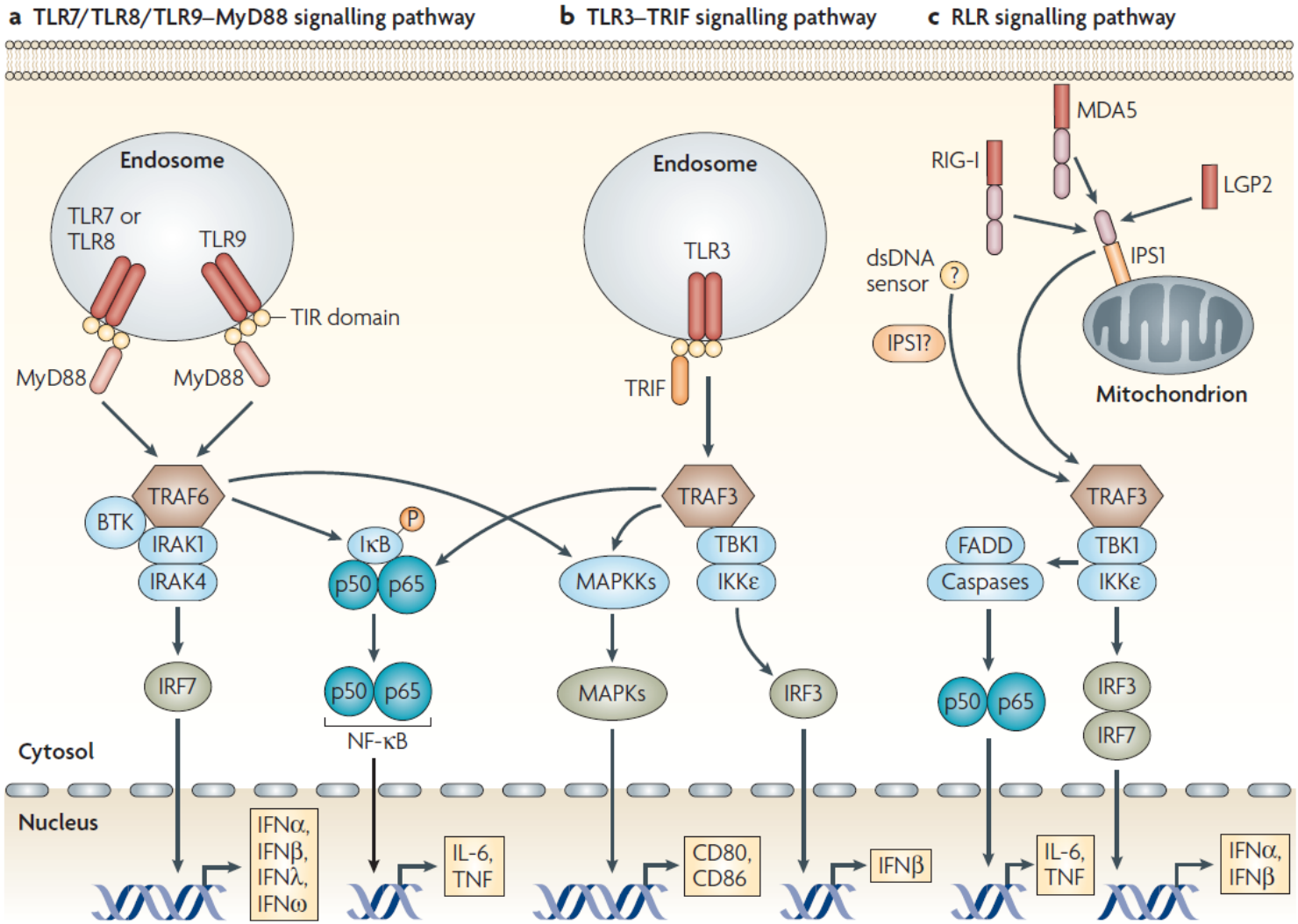
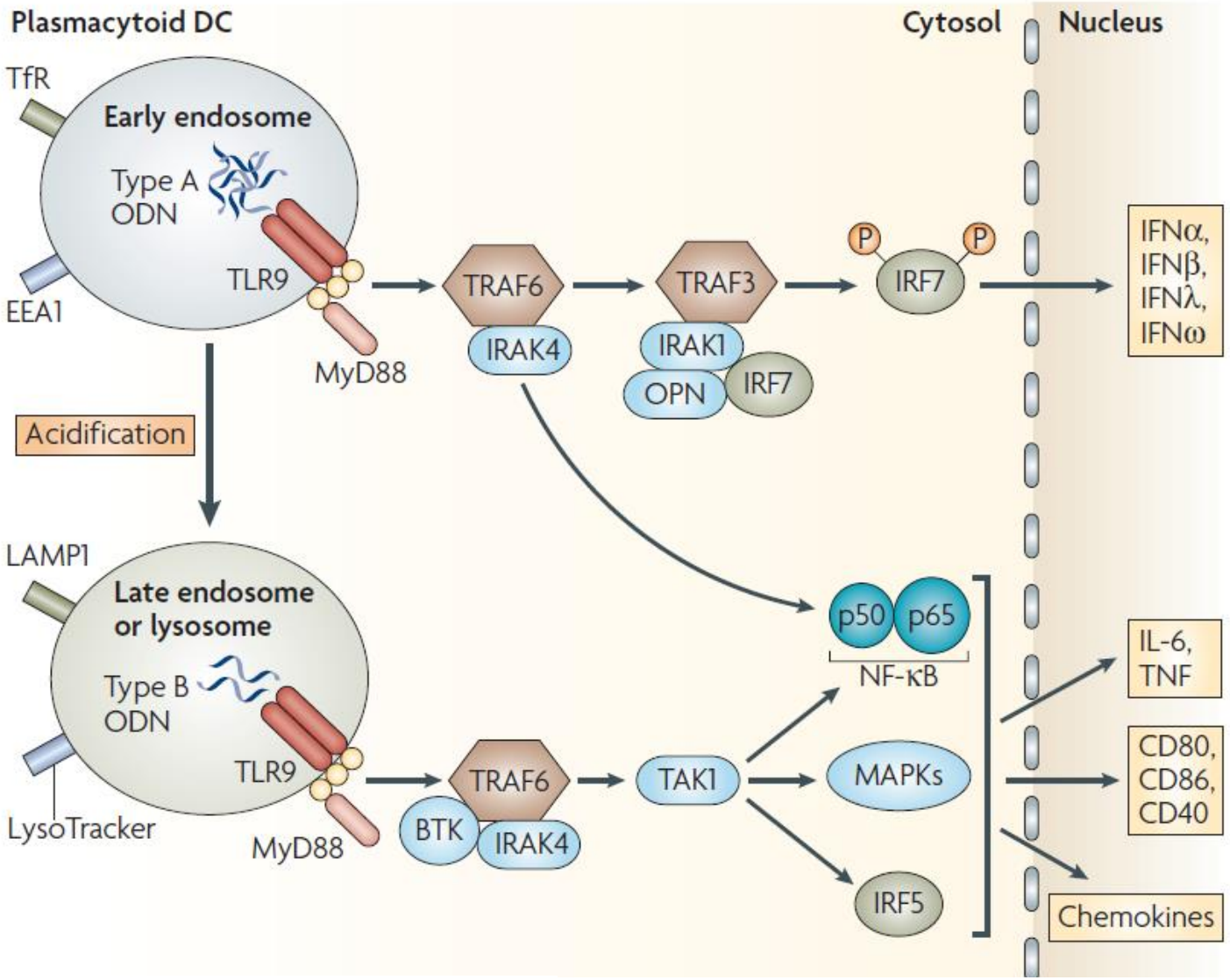
Consultancy fees: *Shanghai Denovo Pharmatech, Nektar, Curetech, Idera, Spring Bank, Array, Memgen*

Biology



Michel Gilliet, Wei Cao* and Yong-Jun Liu* NATURE REVIEWS | IMMUNOLOGY

Biology


Plasmacytoid DC
Cytosol
Nucleus
TfR
Early endosome
Type A ODN
TLR9
EEA1
MyD88
TRAF6
IRAK4
TRAF3
IRAK1
OPN
IRF7
P
P
IRF7
IFNα, IFNβ, IFNλ, IFNω
Acidification
LAMP1
Late endosome or lysosome
Type B ODN
TLR9
LysoTracker
MyD88
TRAF6
BTK
IRAK4
TAK1
p50
p65
NF-κB
MAPKs
IRF5
IL-6, TNF
CD80, CD86, CD40
Chemokines

Biology

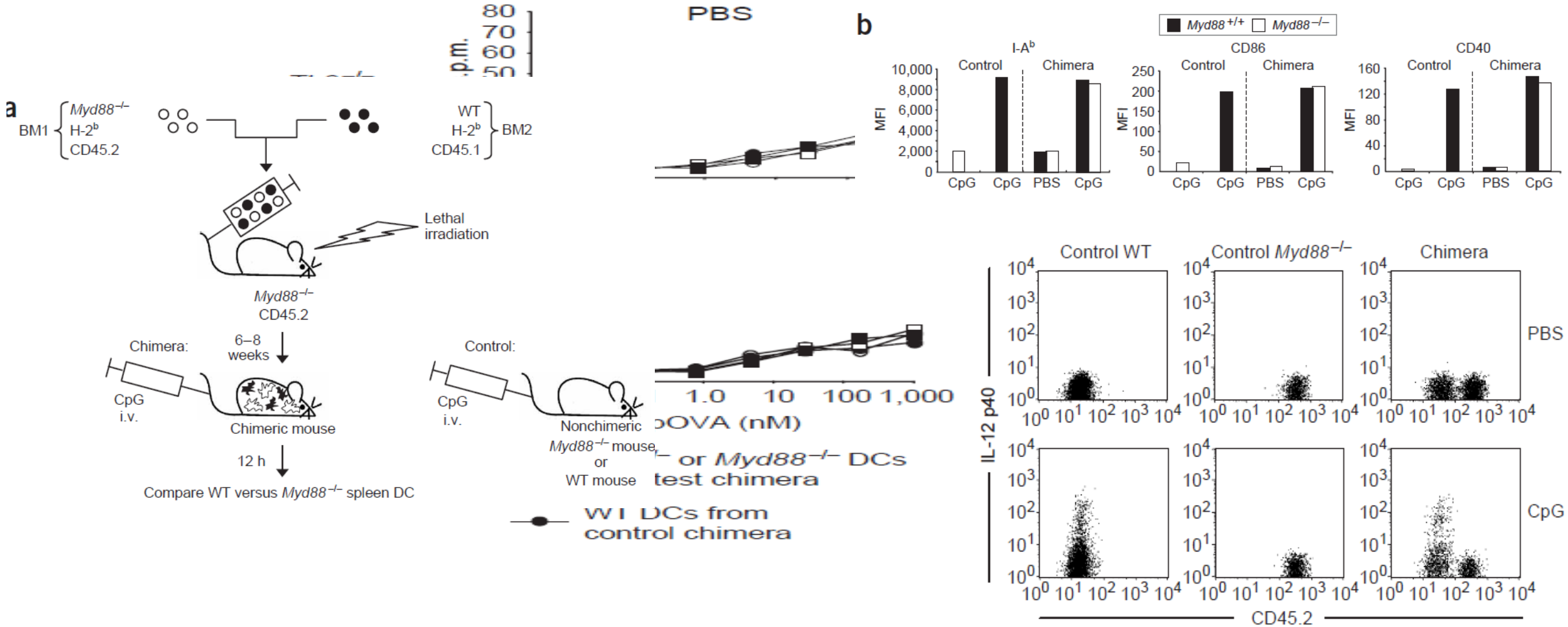
nature immunology

Inflammatory mediators are insufficient for full dendritic cell activation and promote expansion of CD4+ T cell populations lacking helper function

Roman Spörri[1] & Caetano Reis e Sousa

Dendritic cells (DCs) can be activated directly by triggering of receptors for pathogens or, indirectly, by exposure to inflammatory signals. It remains unclear, however, whether the two pathways result in qualitatively similar DCs or lead to equivalent adaptive immune responses. Here we report that indirect activation by inflammatory mediators generated DCs that supported CD4+ T cell clonal expansion but failed to direct T helper cell differentiation. In contrast, exposure to pathogen components resulted in fully activated DCs that promoted T helper responses. These results indicate that inflammation cannot substitute for contact with pathogen components in DC activation and suggest that the function of pattern recognition by DCs is to couple the quality of the adaptive immune response to the nature of the pathogen.

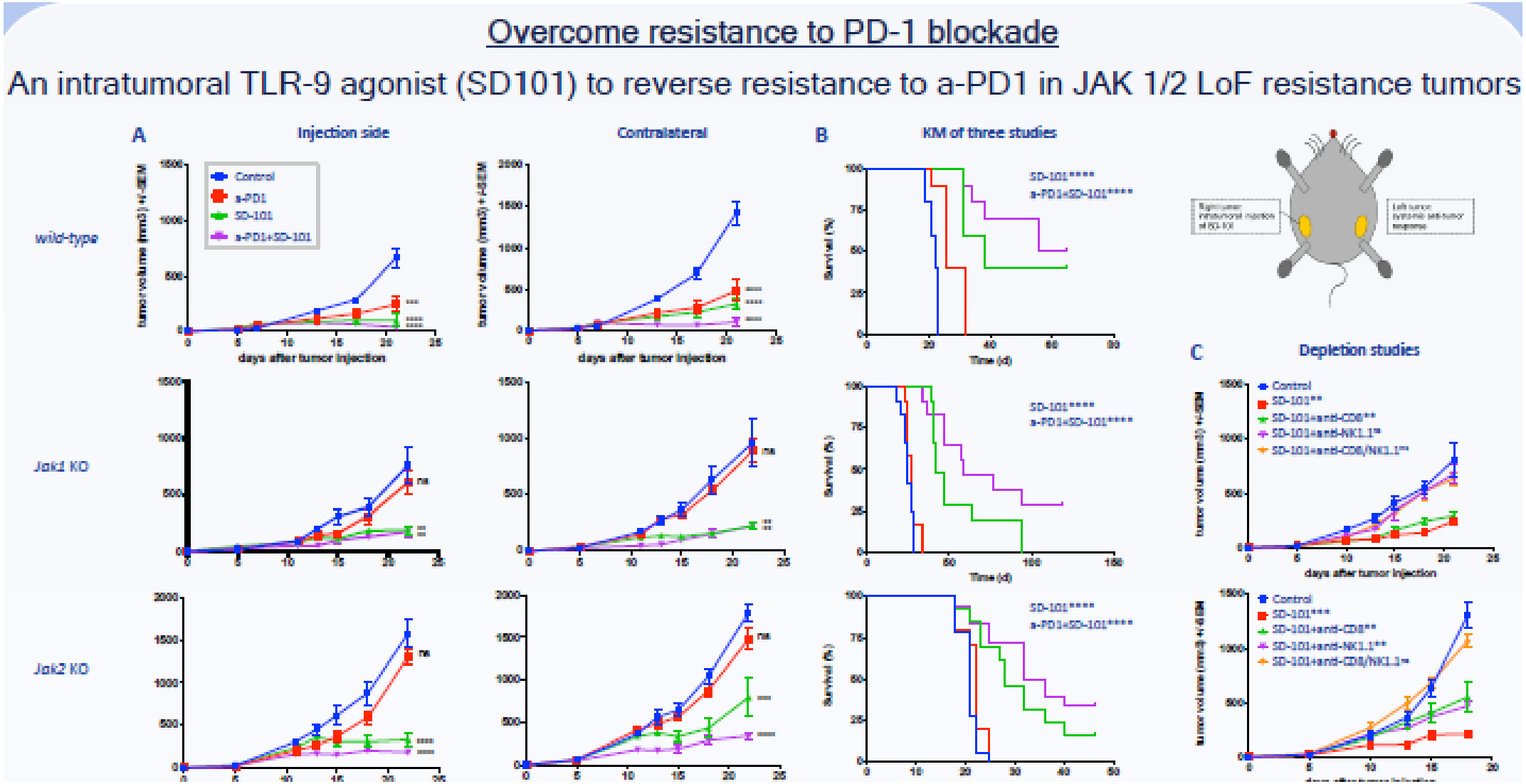
TLR activation is needed for mature and committed immune T cell response



Sporri R et al Nat.Immunology 2004

Biology

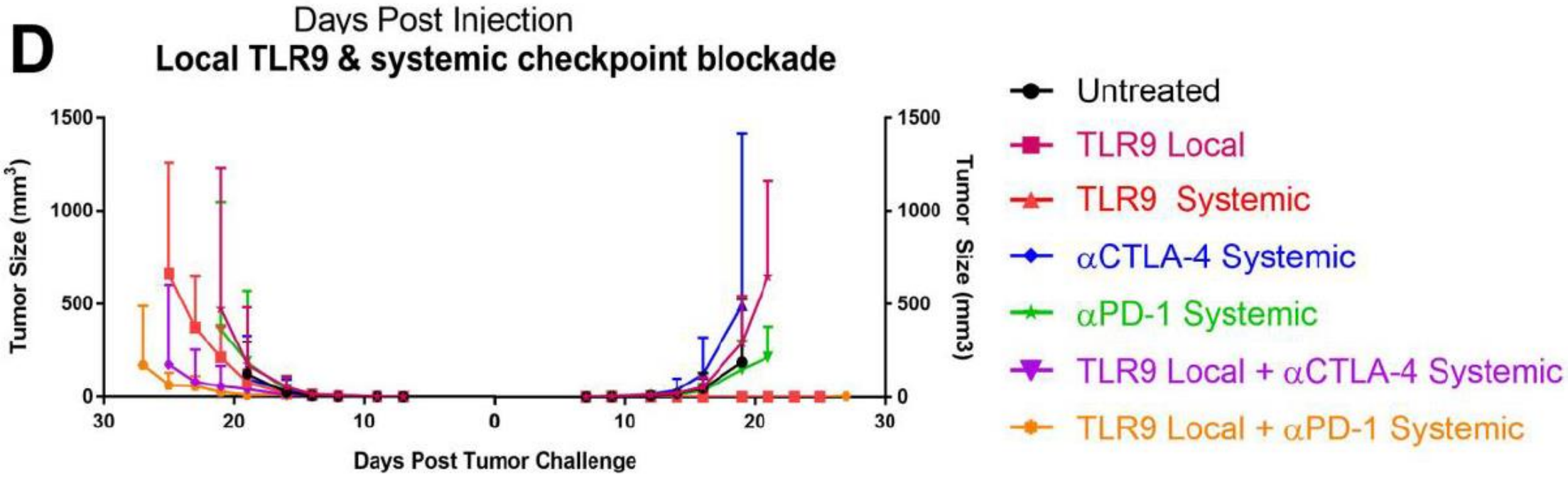
TLR9 activation can overcome resistance PD-1 blockade in preclinical models



Castro DT……Riba A ASCO 2019

Route of Administration

Intratumoral TLR-9 Activation Not Systemic

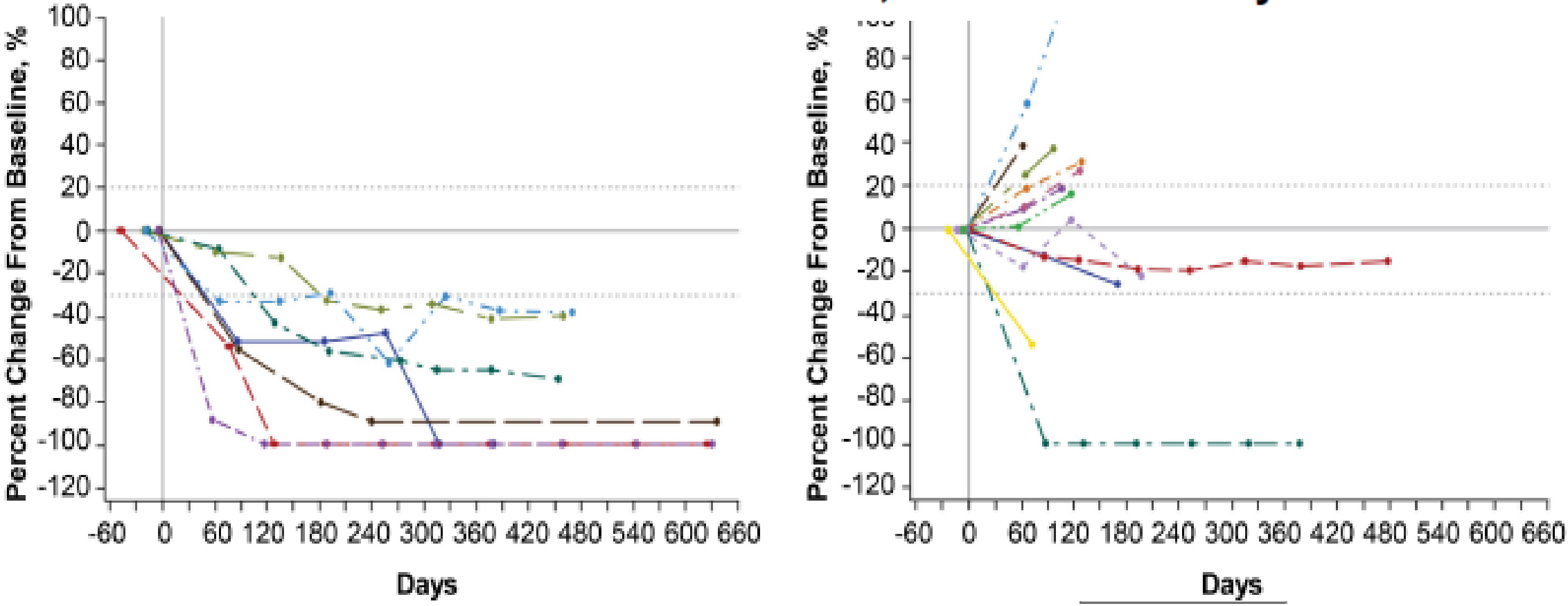


Reilly M … Curran M JITC in press

Clinical activity

Combination with Checkpoint Inhibition

SD-101 in Combination with Pembrolizumab in Advanced Melanoma: Results of a Phase 1b, Multicenter Study

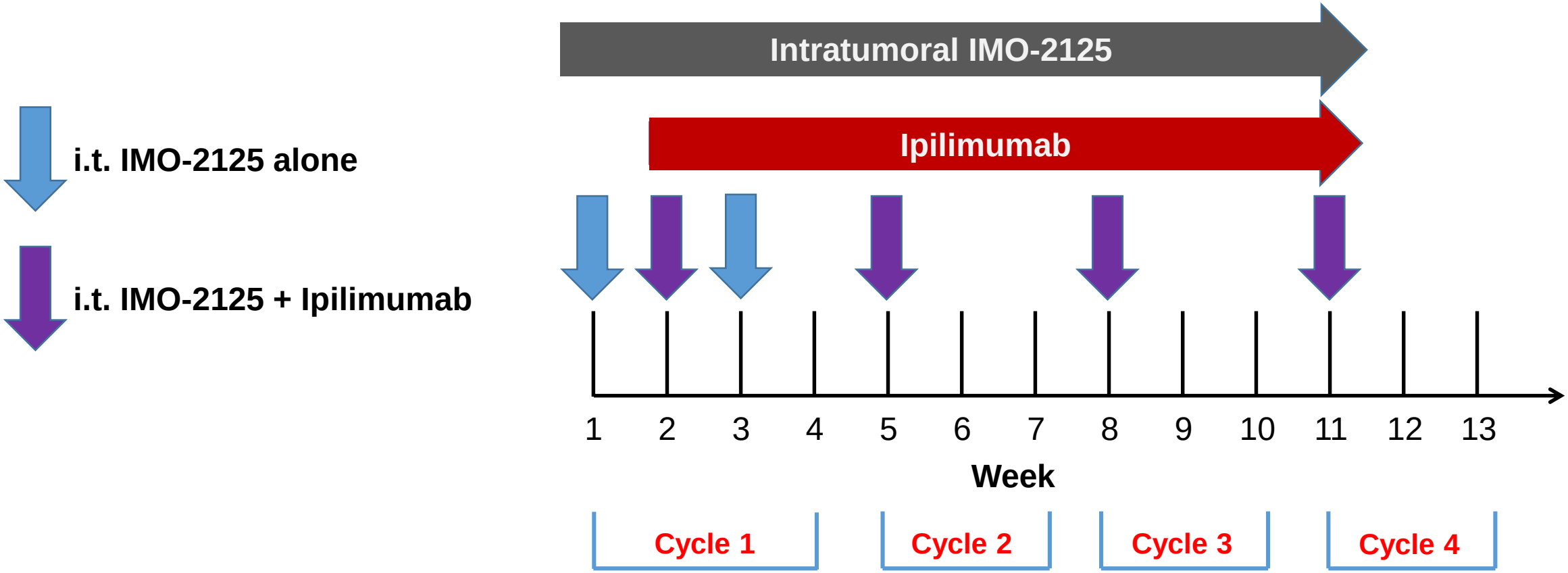


Ribas A Cancer Dicovery 2018

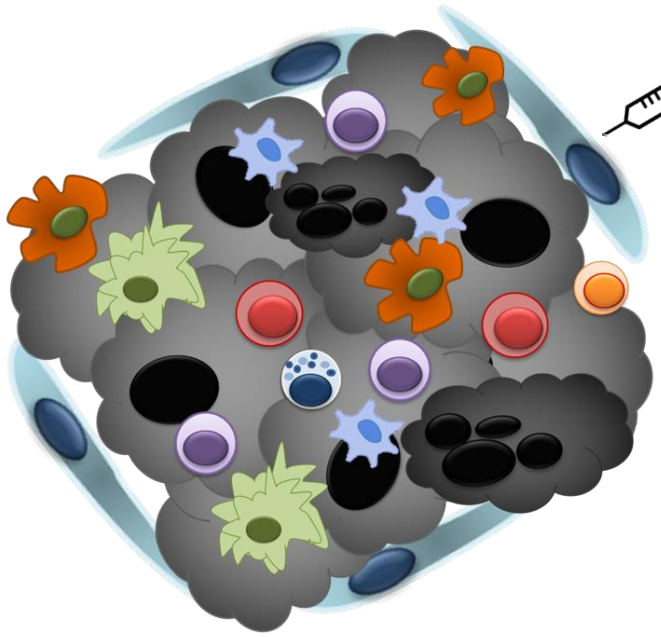
Early and late immune analysis post intratumoral TLR9 agonist (Tilsotolimod) with ipilimumab in patients with anti-PD-1 resistant advanced melanoma

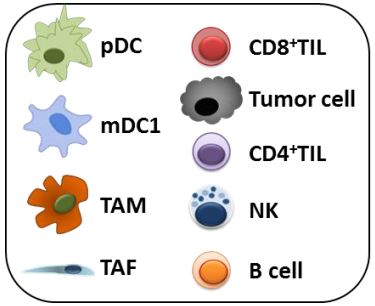
A phase 1/2 study of Intratumoral Tilsotilomod (IMO-2125) in Combination with Ipilimumab in patients with Refractory (anti-PD-1 resistant) Metastatic Melanoma

Trial Design (NCT02644967)

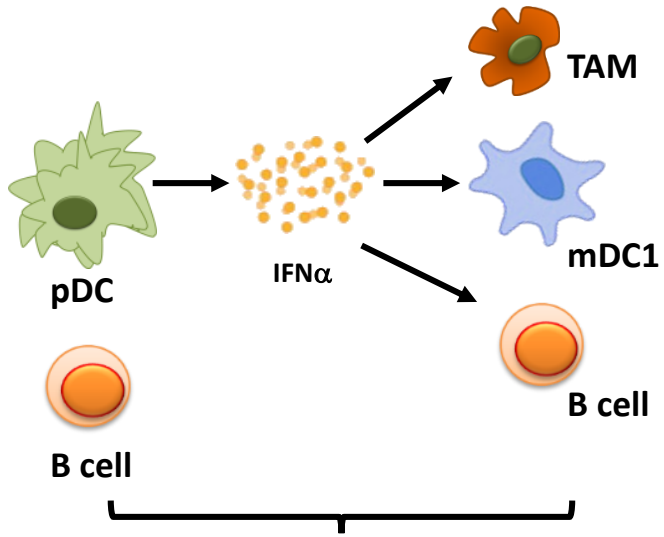


Modulation of the tumor microenvironment by intratumoral administration of the TLR9 agonist Tilsotolimod (IMO-2125)



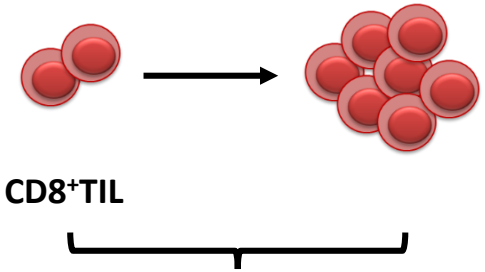


1. TLR9 induction of IFNα and APC maturation



Activation of APCs to improve T-cell priming

2. TIL Activation and Proliferation



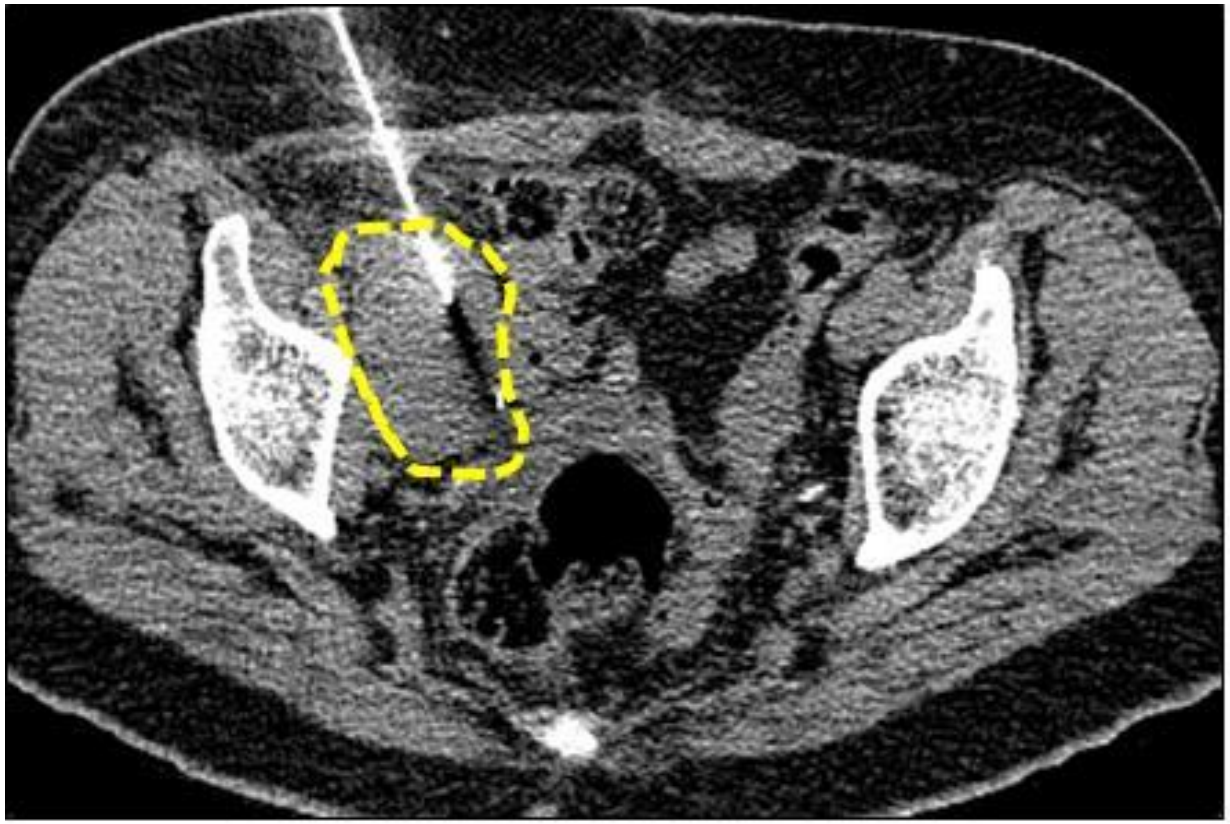
Improved antigen presentation results in TIL activation and proliferation

Patient Characteristics

CHARACTERISTIC	Efficacy Population (N=21)
Age at enrollment – median yr (range)	68 (39-91)
Sex, n (%)	
Male	14 (67)
Female	7 (33)
ECOG performance status n (%)	
0	14 (67)
1	6 (28)
2	1 (5)
Stage n (%)	
III	4 (19)
IV M1a or M1b	10 (48)
IV M1c	7 (33)
Lactate dehydrogenase, n (%)	
≤ ULN	13 (62)
≥ ULN	8 (38)
BRAF V600 Mutation, n (%)	
Positive	10 (47)
Negative	9 (43)
Unknown	2 (10)
Brain Metastases, n (%)	
Yes	2 (10)
No	19 (90)
Visceral Metastases, n (%)	
Yes	15 (72)
No	6 (28)
Prior Treatment, n (%)	
PD(L)-1 inhibitor*	21 (100)
Alone	10 (48)
CTLA-4 inhibitor + PD-1 inhibitor	6 (28)
Other PD(L)-1 combination	5 (24)
CTLA-4 inhibitor*	10 (48)
BRAFi and/or MEKi	2 (10)

Haymaker….Diab et al., under review

Image-guided intratumoral injection of deep lesions with Tilsotilomod



CT guided Intratumoral injection of deep inguinal soft tissue mass

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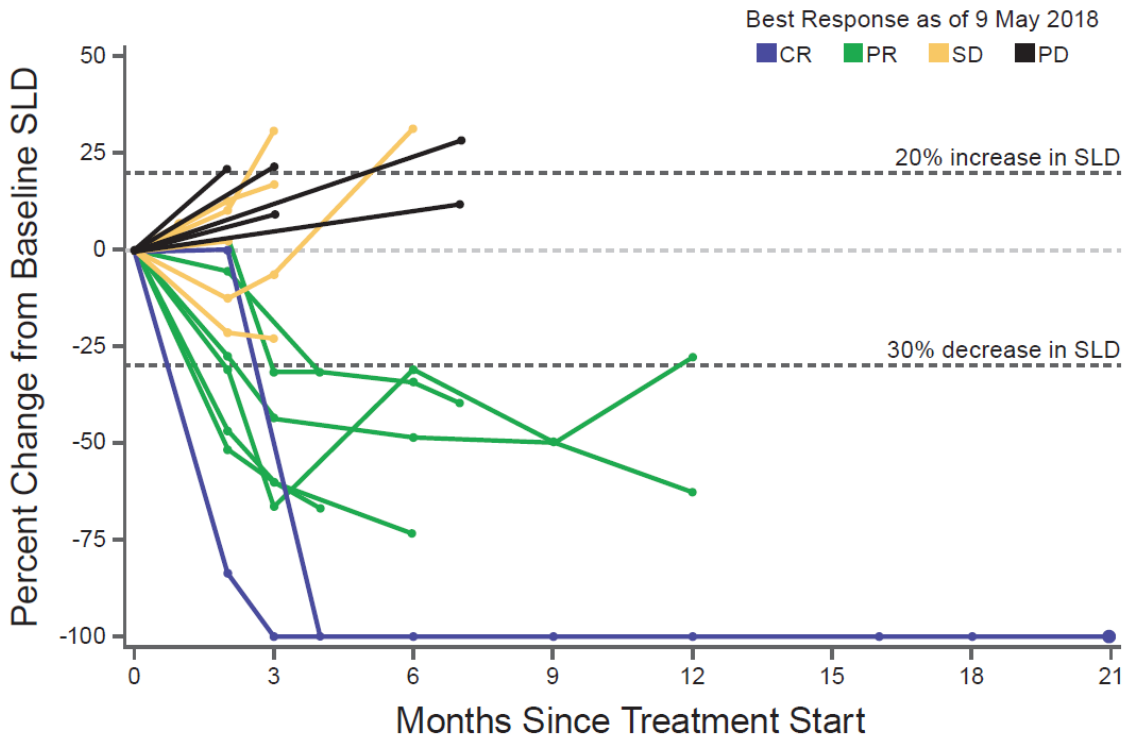
Early response data to Tilsotolimod + Ipilimumab



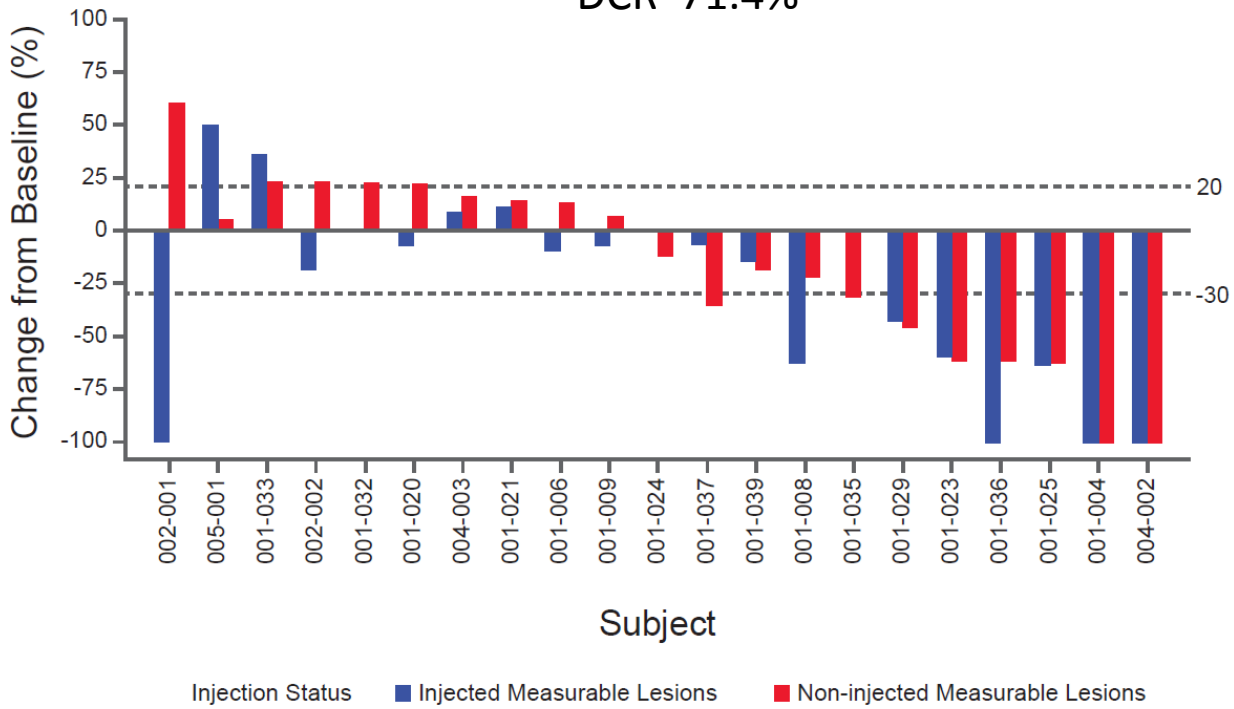
Subjects treated with tilsotolimod 8 mg + ipilimumab with at least 1 post-baseline disease evaluation.

Data cut-off date: 09MAY2018

Produced on 10MAY2018

ORR 38%

DCR 71.4%



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Early response data to IMO-2125 + Ipilimumab

Response	Total (N = 21)	Anti-CTLA-4 Naïve (N = 11)	Anti-CTLA-4 Exposed (N=10)
Objective Response Rate (%)	38	46	30
Partial Response (%)	28	28	30
Complete Response (%)	10	18	0
Stable Disease (%)	38	45	30
Progressive Disease (%)	24	9	40

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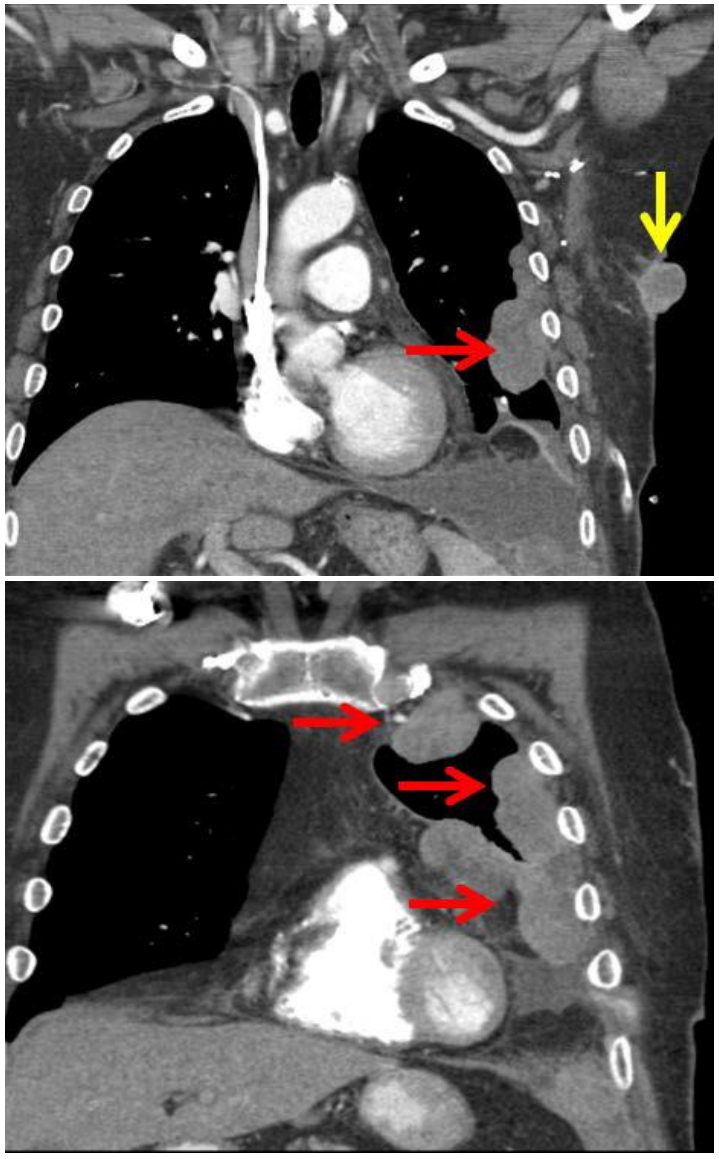
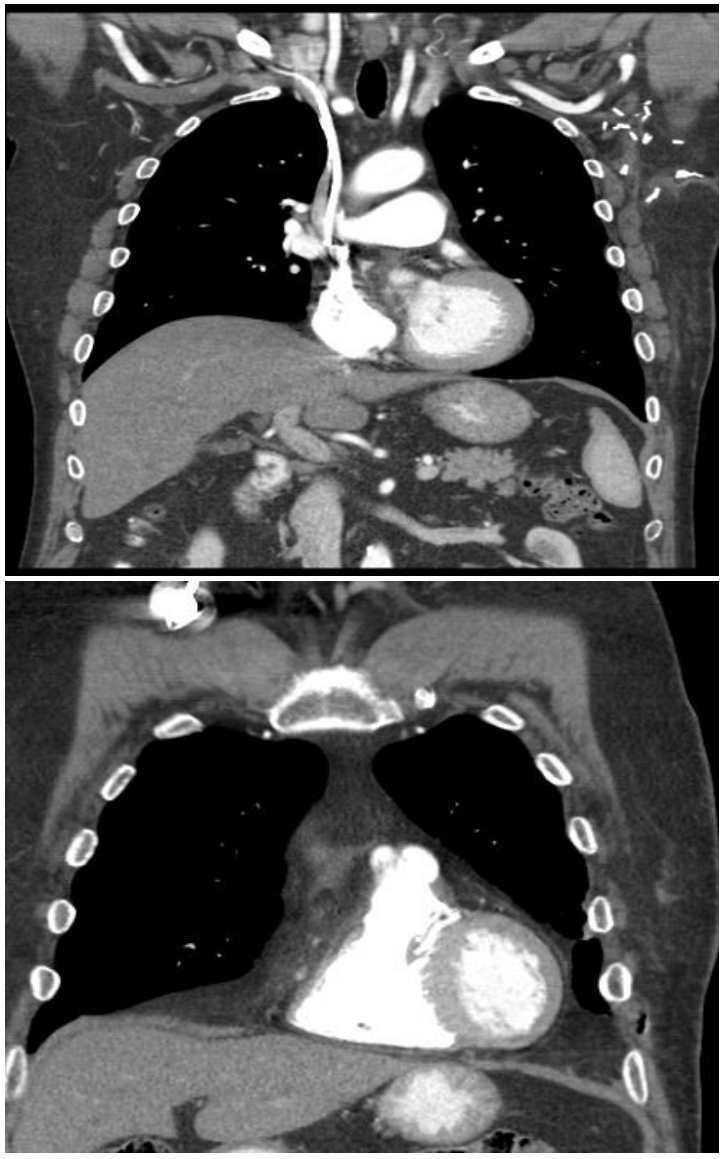
Tumor Imaging of Patient with a Complete Response: Ipilimumab + i.t. Tilsotilomod

Pre-Therapy



Post-Therapy



Injected Lesion

Distant Lesion

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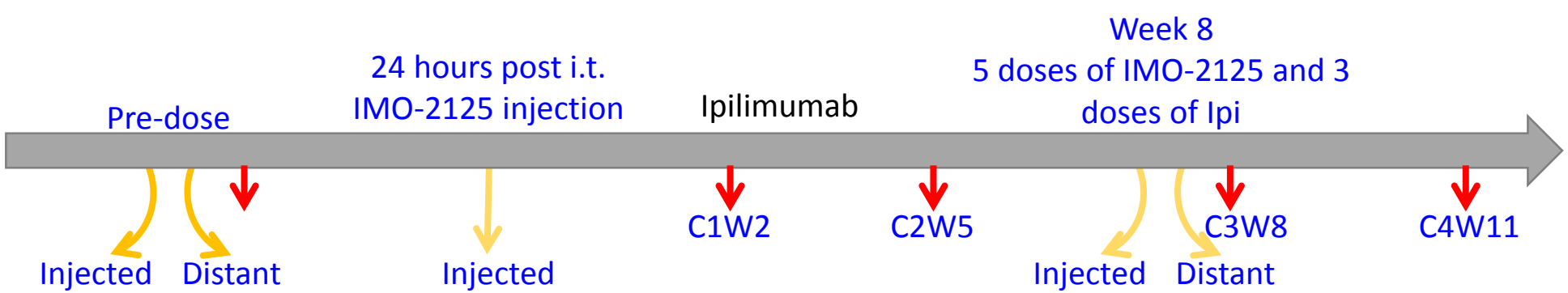
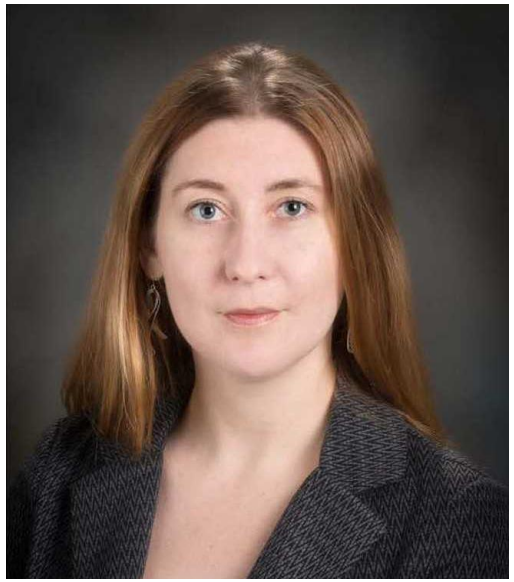
Immune response monitoring to correlate with mechanism of action

Injected = Injected lesion
Distant = Un-injected Lesion

= collection of biopsy

= collection of PBMCs





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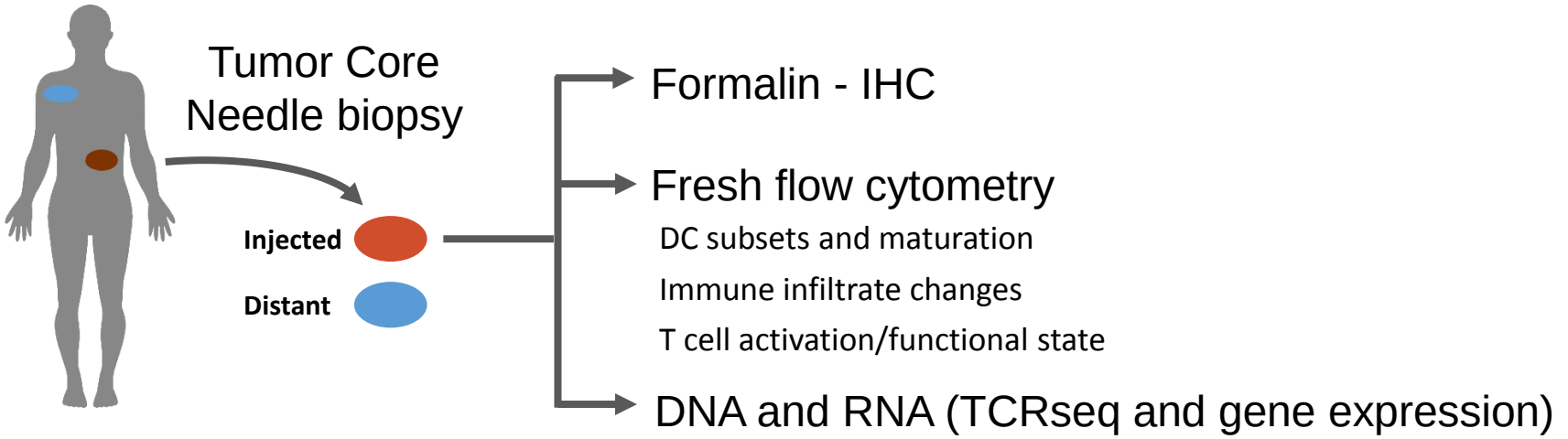
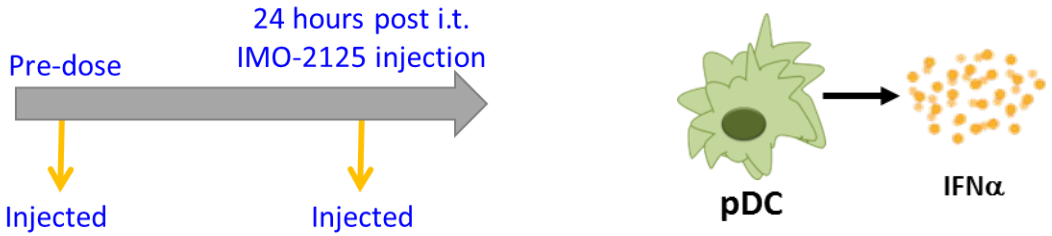
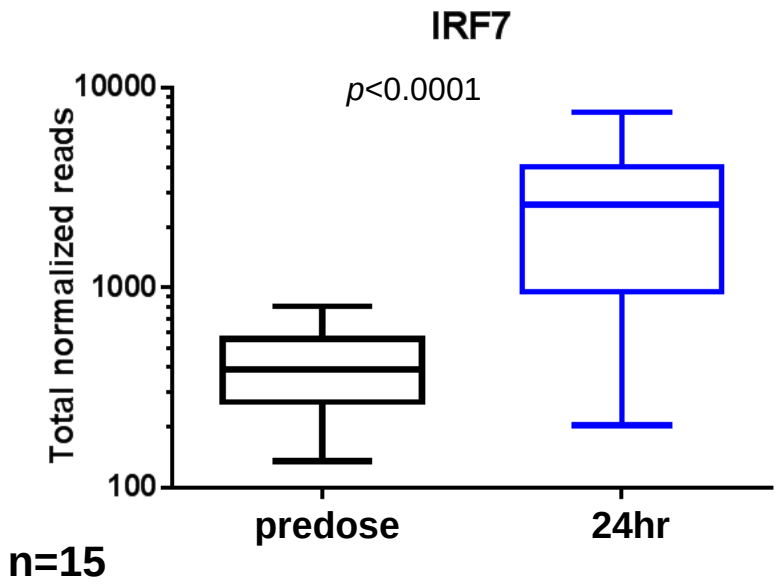
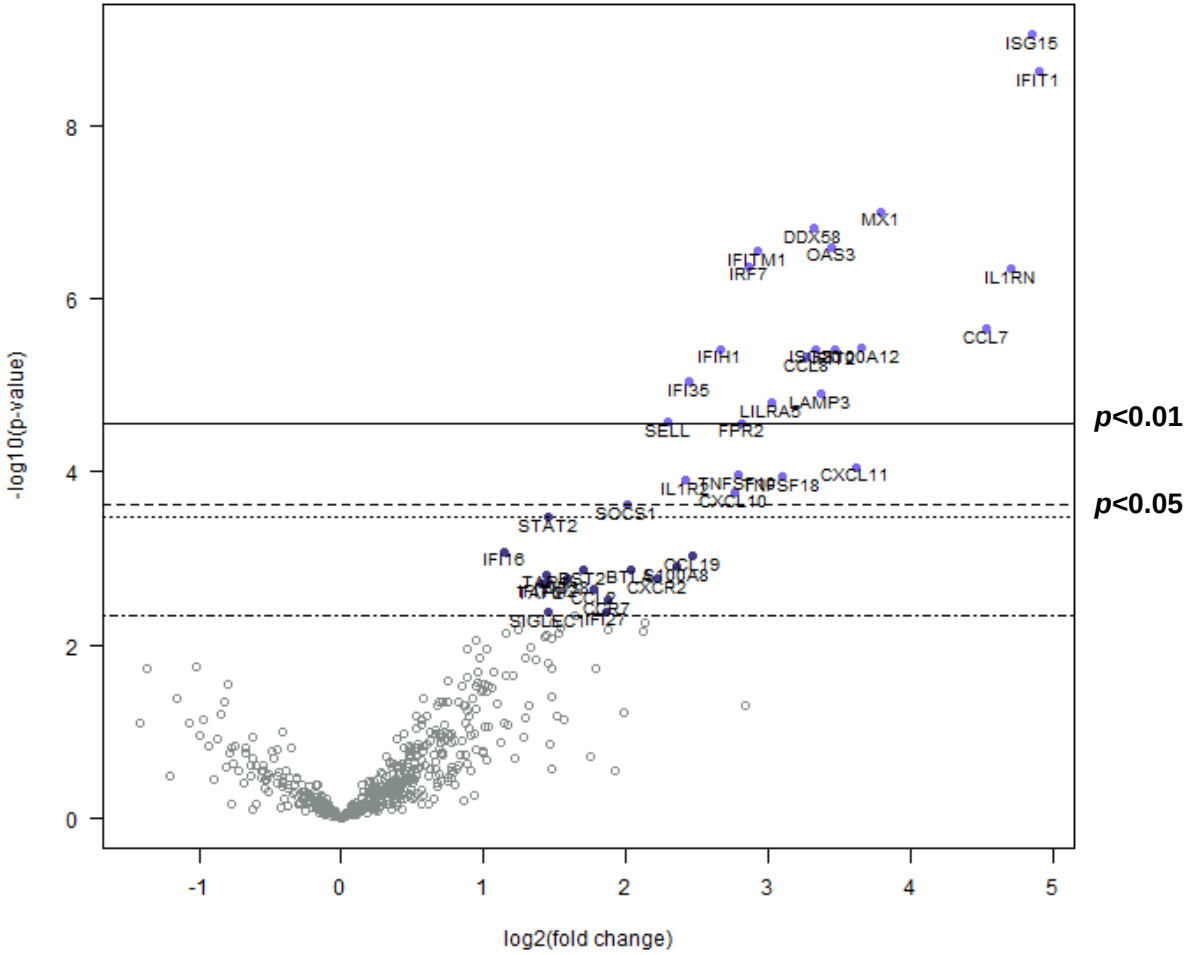


Induction of IFNα-response gene signature after i.t Tilsotilomod







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4062

Activation of Innate and Adaptive Immunity Using Intratumoral Tilsotolimod (IMO-2125) as Monotherapy in Patients With Refractory Solid Tumors: a Phase 1b Study (ILLUMINATE-101)

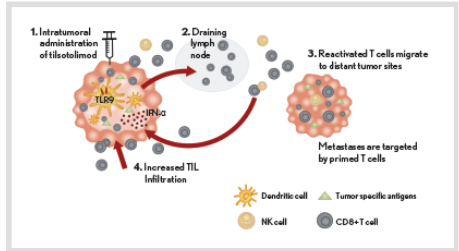
Hani M. Babiker,[†1] Erkut Borazanci,[2] Vivek Subbiah,[3] Orla Maguire,[4] Shah Rahimian,[5] Hans Minderman,[4] Cara L. Haymaker,[3] Chantale Bernatchez,[3] Gurjaap Bindra,[5] Ian Iverson,[5] Srinivas Chunduru,[5] Peter M. Anderson,[6] Igor Puzanov,[4] Adi Diab[3]

[1]University of Arizona Cancer Center, Tucson, AZ; [2]HonorHealth Research Institute, Scottsdale, AZ; [3]University of Texas MD Anderson Cancer Center, Houston, TX; [4]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [5]Idera Pharmaceuticals, Exton, PA; [6]Cleveland Clinic, Cleveland, OH

BACKGROUND

- Tilsotolimod (IMO-2125) is an investigational synthetic toll-like receptor 9 (TLR9) agonist with potent immunostimulating activity (**Figure 1**)[1]
- Preliminary results of a phase 1/2 study of intratumoral tilsotolimod plus ipilimumab in anti-PD-1–refractory advanced melanoma demonstrated durable responses and evidence of an abscopal effect[2]
- ILLUMINATE-101 (NCT03052205) is a phase 1b study that further explores the role of single-agent tilsotolimod in modulating the tumor immune microenvironment (TME) in patients with solid tumors

Figure 1. Tilsotolimod Mechanism of Action

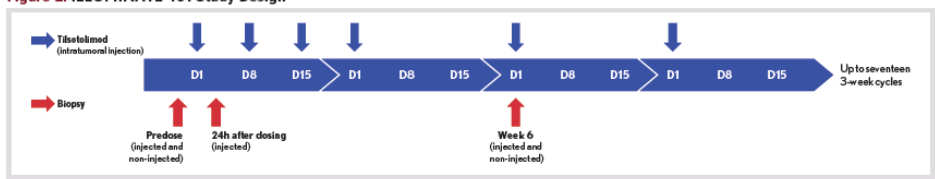


IFN-α, interferon-alpha; NK, natural killer cell; TIL, tumor infiltrating lymphocyte.

METHODS

- Adults with a histologically or cytologically confirmed diagnosis of metastatic refractory solid tumors were eligible
- Patients were to be enrolled into 4 dose cohorts (n ≈ 8 each) and receive intratumoral tilsotolimod in escalating doses (8 mg, 16 mg, 23 mg, and 32 mg) into a single lesion (**Figure 2**)
- If > 2 patients in a cohort experienced DLTs, enrollment at that dose level was to be stopped pending cohort review committee recommendations on further study conduct
- An additional 8 patients were to be enrolled at the recommended phase 2 dose (RP2D)
- Tumor biopsies of injected (primary) and distant lesions were obtained at baseline and at 24 hours and 6 weeks after dosing (on treatment)

Figure 2. ILLUMINATE-101 Study Design



- Immune analyses included NanoString® (NanoString Technologies, Seattle, WA) and/or flow cytometry of type 1 interferon (IFN) pathway activation, IFN-γ levels, activation of dendritic cell subsets, and changes in T-cell status
  - Gene set scores were generated from the PanCancer Immune (PCI) Profiling Panel (NanoString Technologies, Seattle, WA)
- Primary objective of dose evaluation: safety
- Secondary objectives: establish RP2D; assess clinical activity, pharmacokinetics, and alterations in TME
- Exploratory objective: evaluate immunologic activity

RESULTS

- As of February 28, 2019, 54 patients have been enrolled, including 38 in the dose-evaluation portion and 16 in a melanoma dose-expansion cohort (**Figure 3; Table 1**)

Figure 3. Patient Disposition by Tumor Type (A), and Dose Cohort (B)

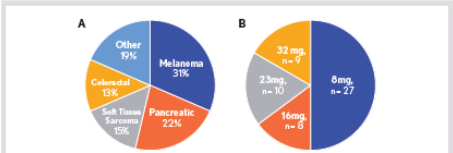


Table 1. Demographics and Baseline Characteristics

Characteristic	N = 54
Median age (range), years	61 (18-86)
ECOG PS 0-1 , n (%)	54 (100)
Elevated LDH, n (%)	17 (32)
Stage IV disease, n (%)	45 (83)
Prior treatment, n (%)	54 (100)
Chemotherapy	38 (70)
Anti–PD-1	18 (33)
Targeted therapy	16 (30)
Anti-CTLA4	8 (15)
Anti–PD-1 + anti-CTLA4	6 (11)
mAb	3 (6)
Other	12 (22)

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; mAb, monoclonal antibody; PD, programmed death.

Safety

- No DLTs or treatment-related adverse events were observed
- No treatment-emergent adverse events (TEAEs) leading to treatment or study discontinuation or death occurred (**Table 2**)

Table 2. Most Common TEAEs

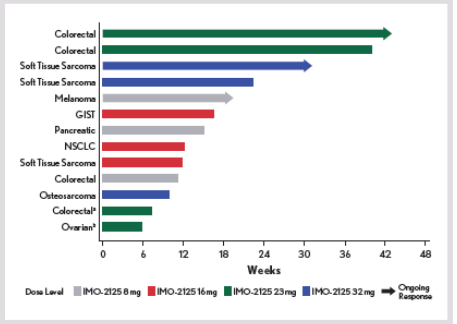
Adverse Event	N = 54
≥ 1 TEAE, n (%)	52 (96)
≥ 1 grade 3/4 TEAE, n (%)	30 (56)
Most common TEAEs, n (%)	
Pyrexia	32 (59)
Fatigue	18 (33)
Chills	14 (26)
Nausea	14 (26)
Vomiting	10 (19)

- The most common grade 3/4 TEAEs were anemia, hyponatremia, pain, sepsis (n = 3 each), fatigue, and thrombocytopenia (n = 2 each)

Efficacy

- Of 29 evaluable patients, 13 (45%) had a RECIST V1.1 disease assessment of stable disease (SD), with a disease control rate of 45%
- Duration of SD ranged from 1.3 to 9.7+ months from start of treatment, with 3 patients ongoing (**Figure 4**)
- No correlations between dose and efficacy were apparent

Figure 4. Duration of Stable Disease by Tumor Type



GIST, gastrointestinal stromal tumor; NSCLC, non-small-cell lung cancer.
*Patient had 1 disease assessment and then withdrew consent "to explore other treatment options". *Patient had 2 disease assessments and then withdrew from study due to "lack of clinical benefit".

Immune Monitoring

- Fresh flow cytometry of samples from 3 patients showed 2 with HLA-DR (MHC Class II) upregulation at 24 hours compared with pretreatment
- Robust activation of type I IFN pathway was observed, demonstrated by increased IRF7, IFIT1, and IFIT2 gene expression, and early increases in type I IFN signaling

Figure 5. Gene Expression Change From Baseline to 24 Hours After Dosing

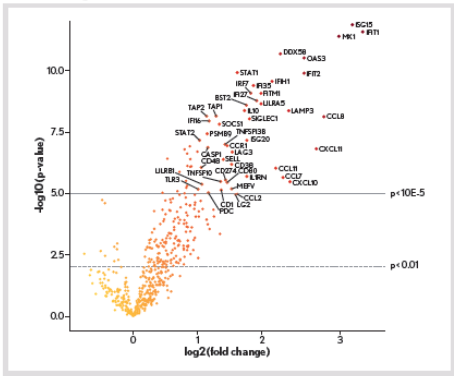
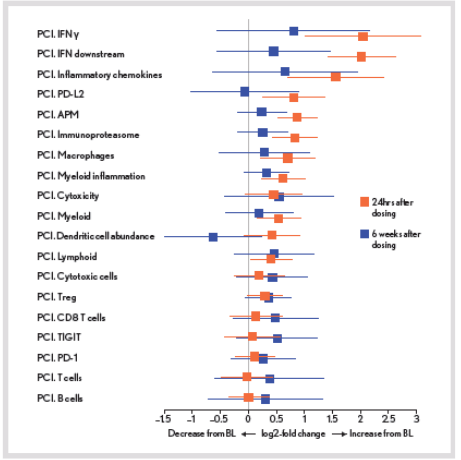
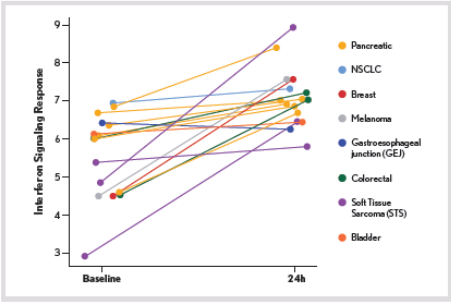


Figure 6. PanCancer Immune Profiling Gene Expression Changes From Baseline for Key Gene Families



The gene set scores were generated from the PanCancer Immune (PCI) Profiling panel.
APM, antigen processing machinery; BL, baseline; PD-L2, programmed death ligand 2; TIGIT, T cell immunoreceptor and Ig and ITIM domains.

Figure 7. IFN-α Signaling Change From Baseline by NanoString



CONCLUSIONS

- Intratumoral injection of single-agent tilsotolimod was well tolerated and showed preliminary evidence of clinical activity across multiple solid tumors, including those traditionally unresponsive to immunotherapy
- Tilsotolimod rapidly increased dendritic cell activation, upregulation of MHC Class II, and upregulation of IFN-α signaling, suggesting improved antigen presentation
- Tilsotolimod-induced upregulation of antigen presentation was observed across multiple tumor types; changes were consistent with those observed in a previous phase 1/2 clinical trial of patients with metastatic melanoma[2,3]
- Based on these data a phase 2 study of tilsotolimod plus nivolumab and ipilimumab has been initiated for the treatment of certain solid tumors (ILLUMINATE-206; NCT03865082)

REFERENCES

1. Wang D, et al. *Int J Oncol.* 2018;53(3):1193-1203.
2. Diab A, et al. *Ann Oncol.* 2018;29(suppl_8): viii442-viii466.10.1093/annonc/mdy289.
3. Haymaker C, et al. Presented at the Society for the Immunotherapy of Cancer Annual Meeting. November 8-12, 2017; National Harbor, MD [abstract O18].

ACKNOWLEDGMENTS

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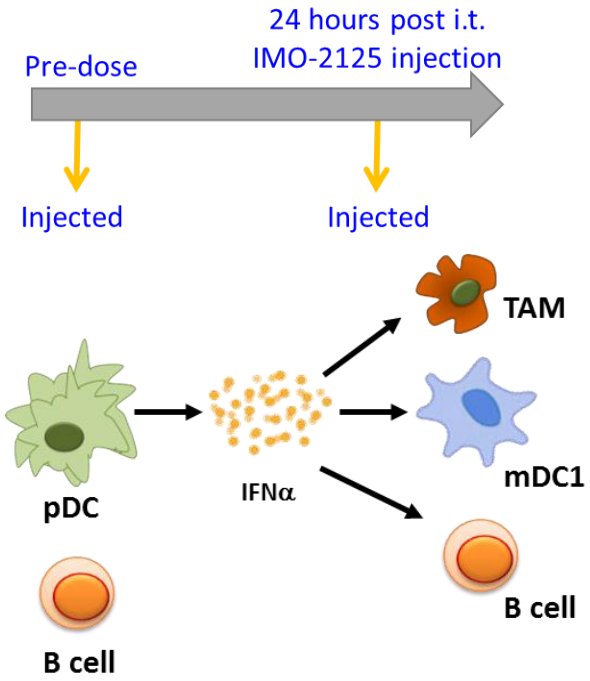
DISCLOSURES

Babiker: none. **Borazanci:** none. **Subbiah:** Idera Pharmaceuticals, Blue Print Medicines, Loxo Oncology, Novartis Oncology, Bayer. **Maguire:** none. **Rahimian:** Idera Pharmaceuticals. **Minderman:** none. **Haymaker:** Idera Pharmaceuticals. **Bernatchez:** Idera Pharmaceuticals. **Bindra:** Idera Pharmaceuticals. **Iverson:** none. **Chunduru:** Idera Pharmaceuticals. **Anderson:** none. **Puzanov:** none. **Diab:** Idera Pharmaceuticals, Nektar Therapeutics, Bristol-Myers Squibb, Jounce Therapeutics, Novartis Pharmaceuticals, Array Biopharma.

†Corresponding author (hanibabiker@email.arizona.edu).

Presented at American Association for Cancer Research Annual Meeting; March 29-April 3, 2019; Atlanta, GA [abstract 4062]. IderaPharma.com

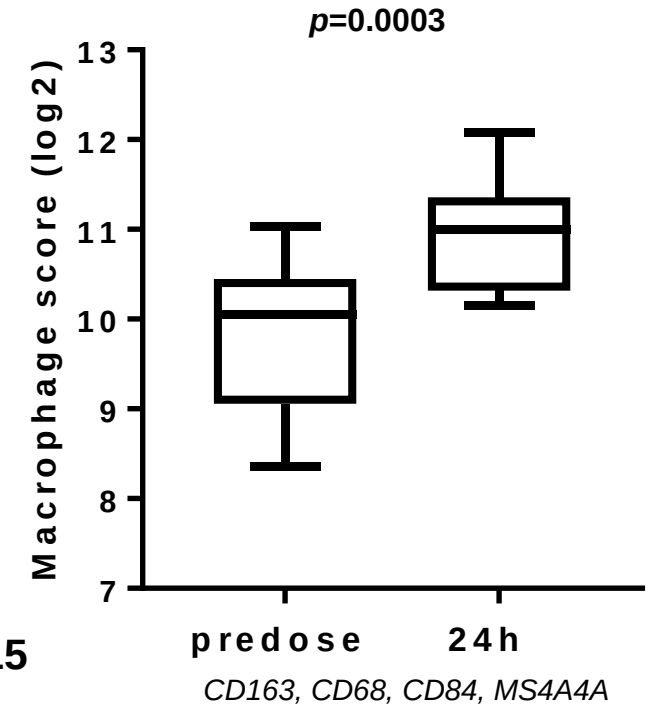
Rapid mDC1 maturation and macrophage influx induced by Tilsotilomod in the tumor



Genes of interest

TAP1/TAP2
PSMB9
IL12
CD80
CCL7/CCL8

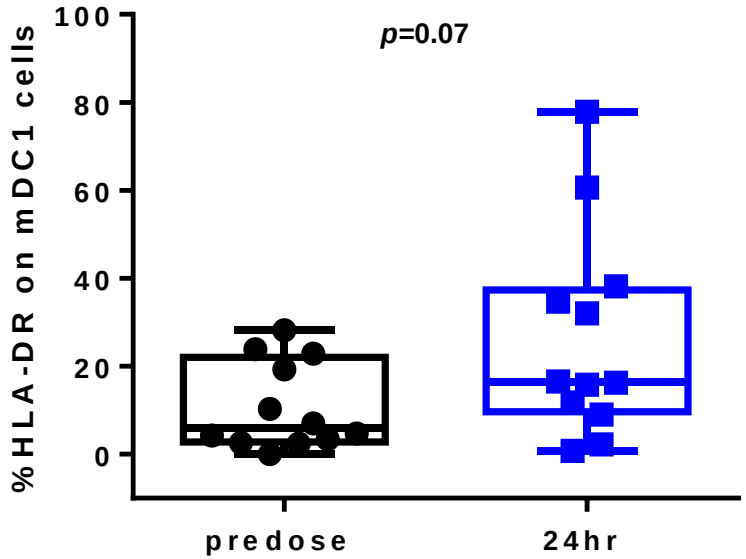
Nanostring



n=15

CD163, CD68, CD84, MS4A4A

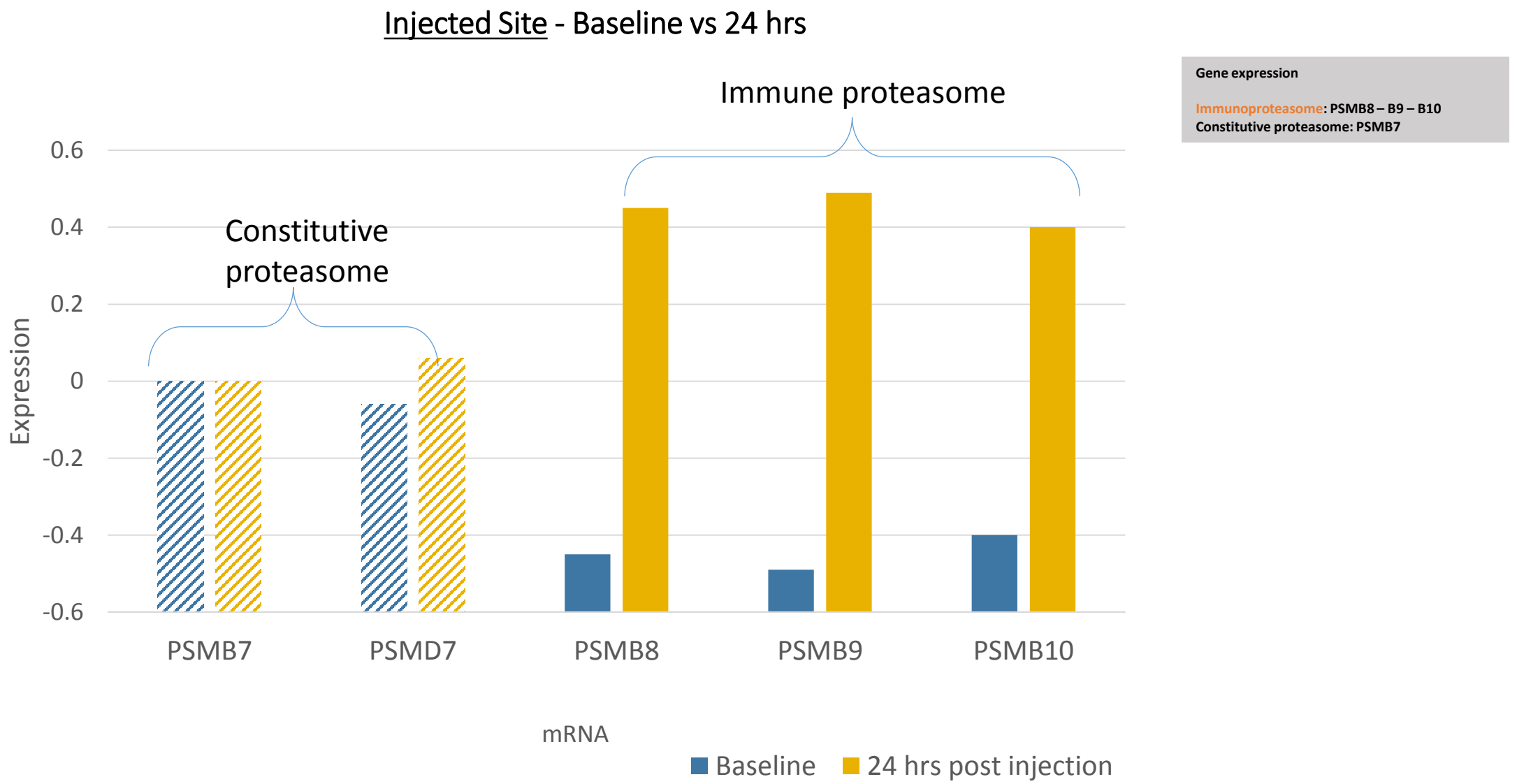
Flow cytometry



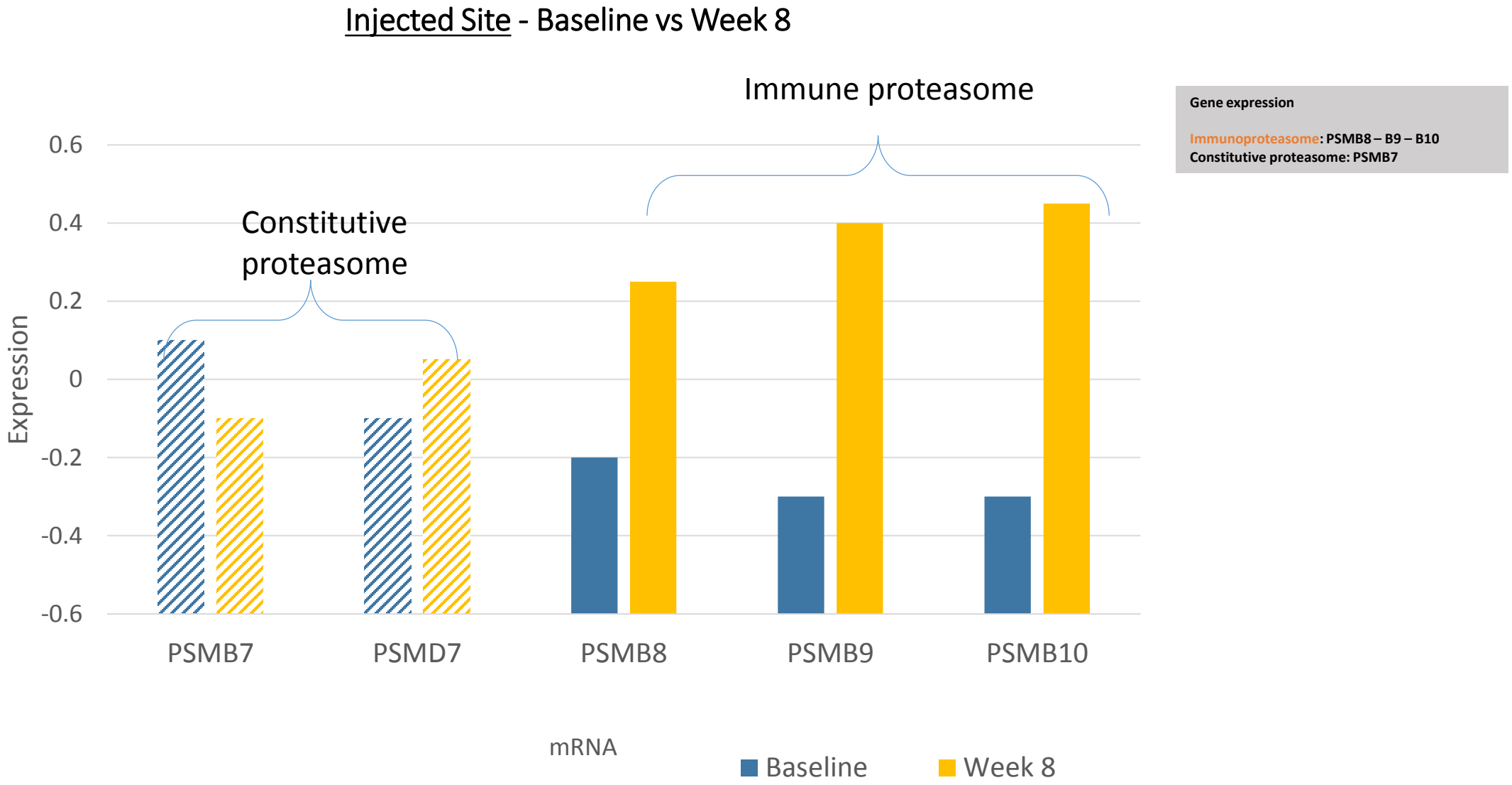
n=12

Haymaker….Diab et al., under review

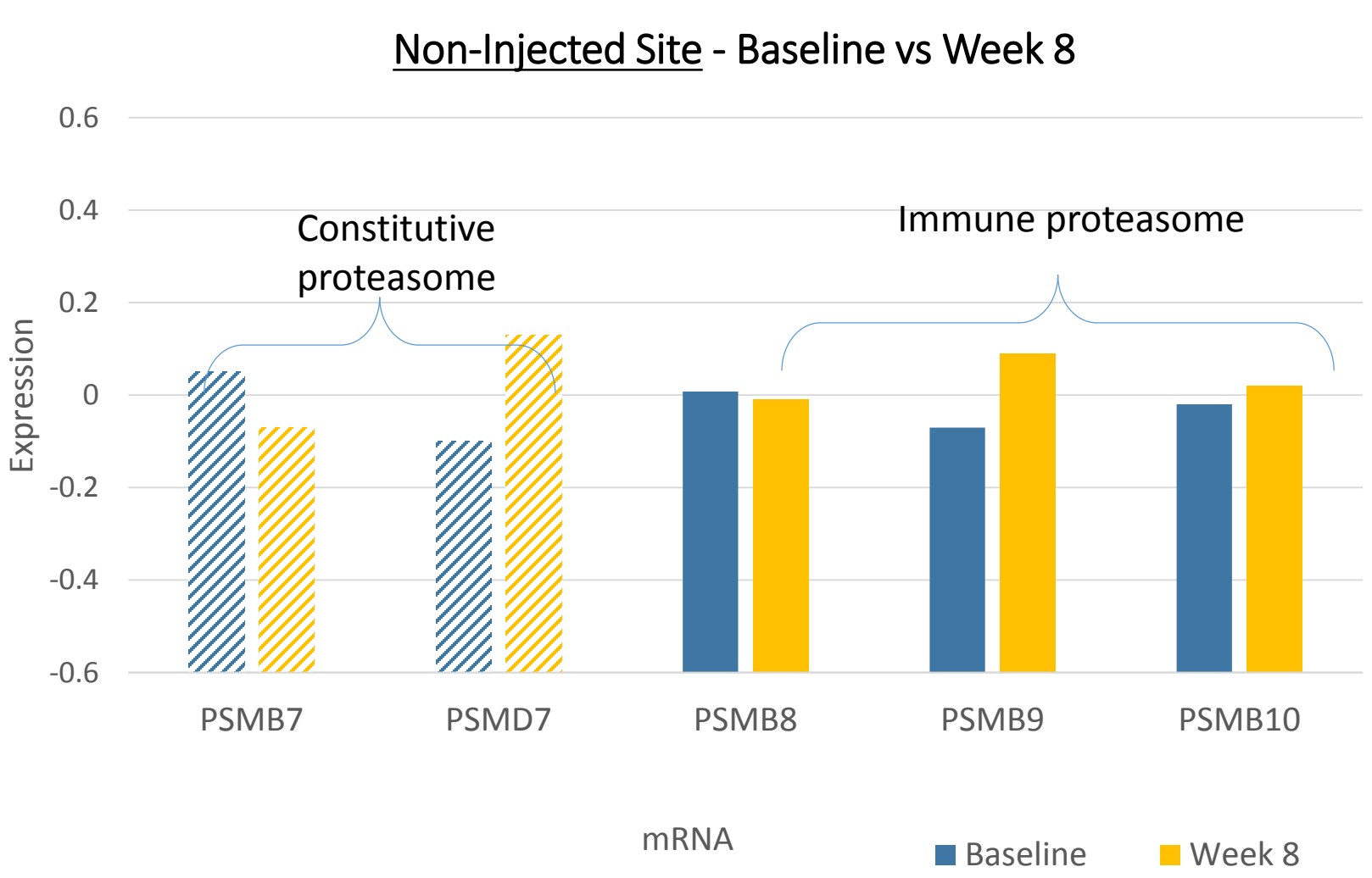
Induction of Antigen Presentation Related Gene Expression



Induction of Antigen Presentation Related Gene Expression

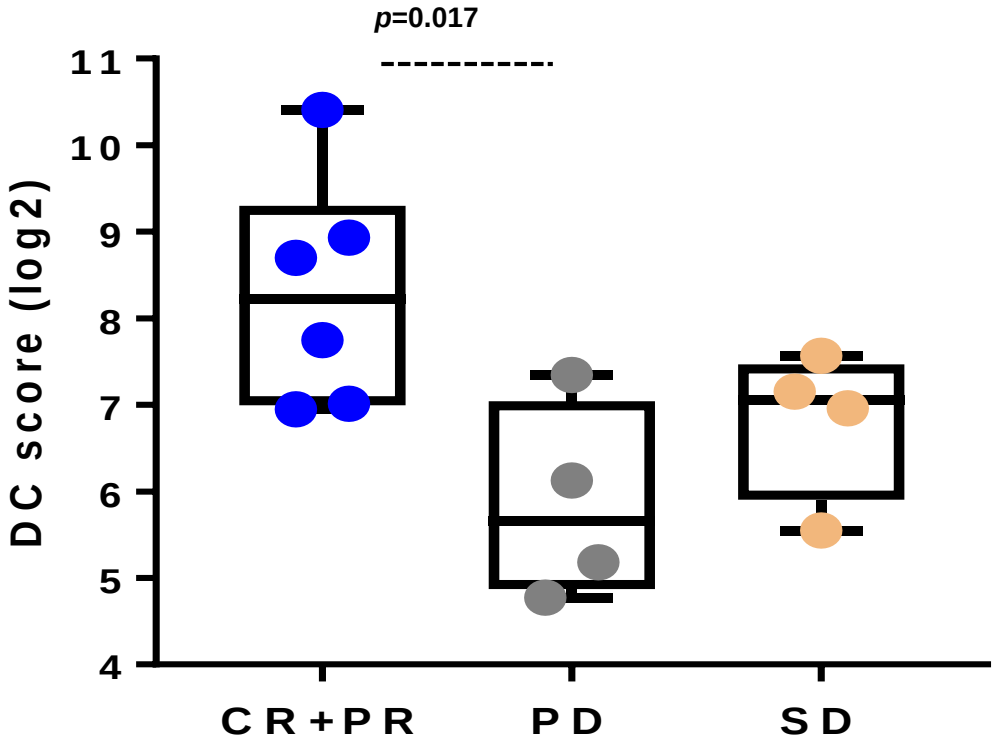


Induction of Antigen Presentation Related Gene Expression



Gene expression

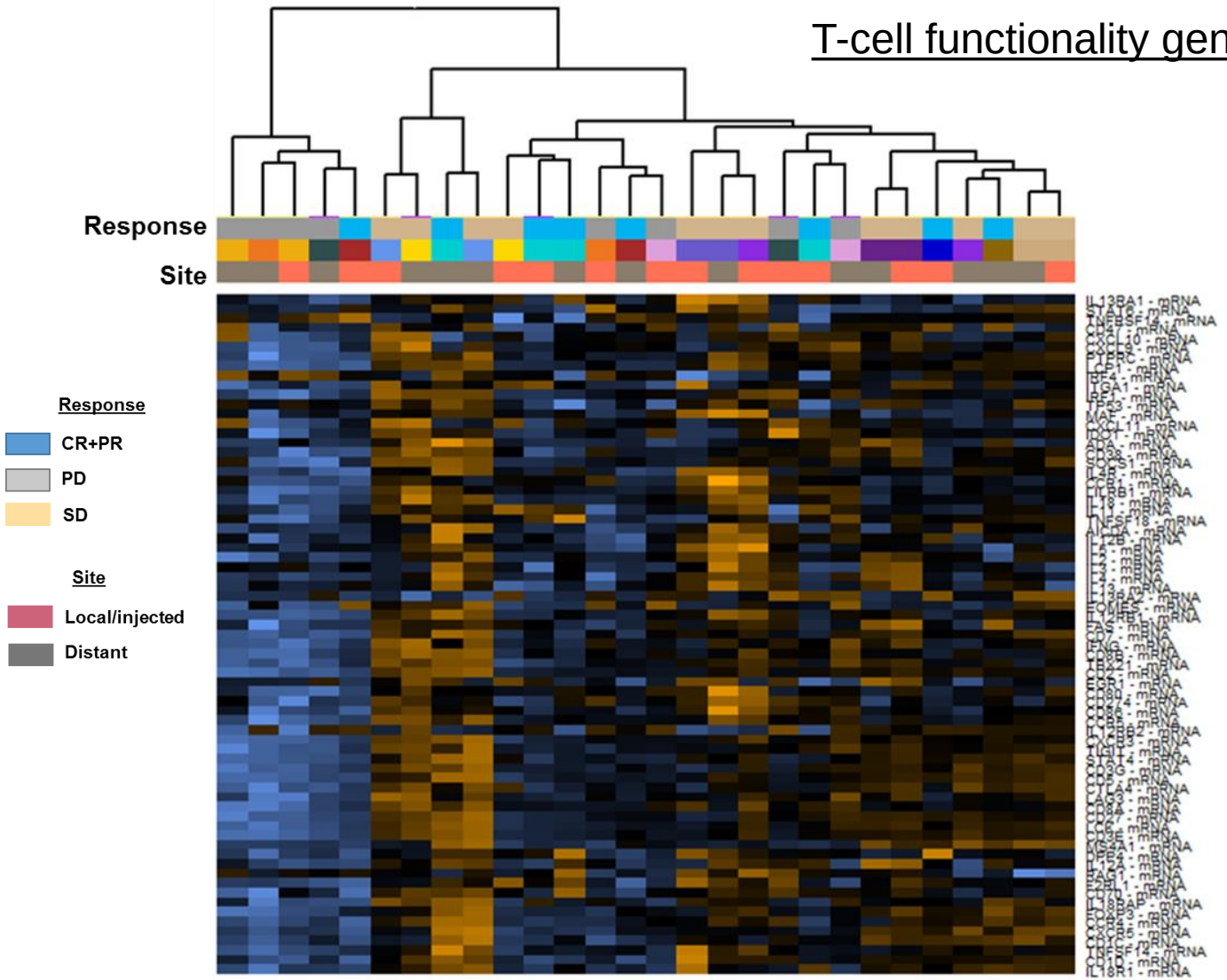
Immunoproteasome: PSMB8 – B9 – B10
Constitutive proteasome: PSMB7



CCL13, CD209, HSD11B1

Haymaker….Diab et al., under review

Are non-responding patients' tumors "immunologically cold"?



Haymaker et al., under review

Sharma et al., 2017 *Cell*
Tumeh et al., 2014 *Nature*

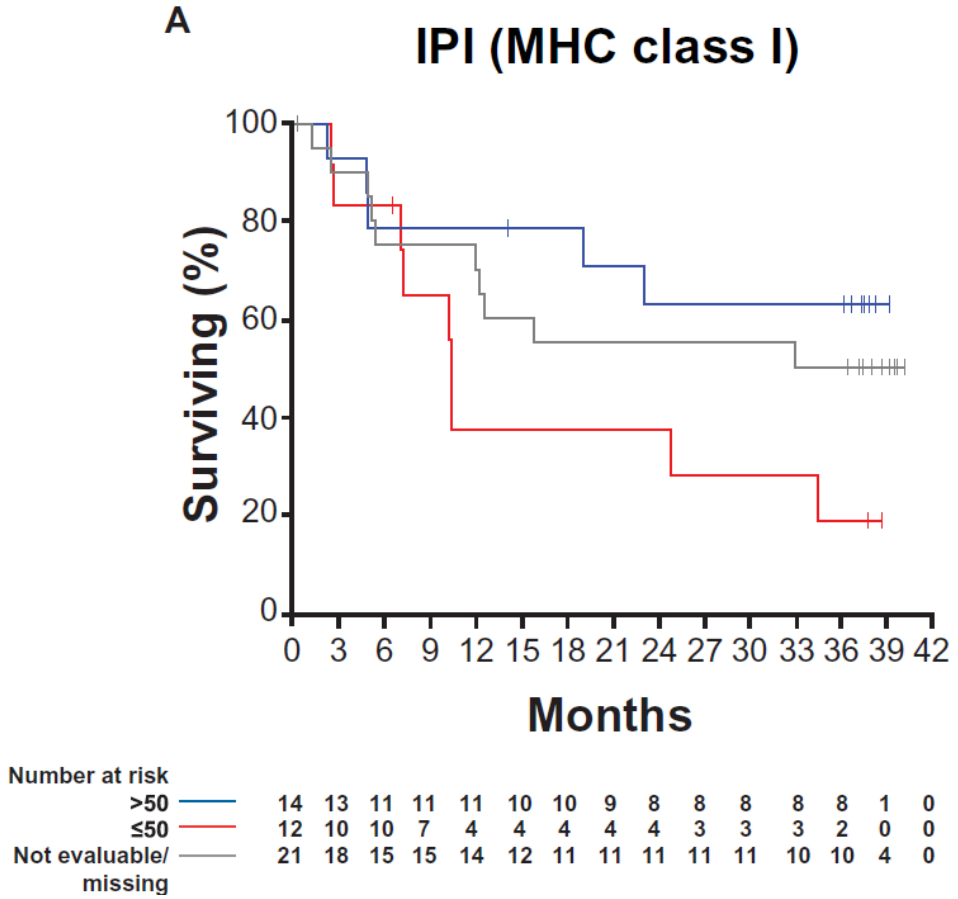
Single agent anti-CTLA4 requires robust MHC class I

CANCER

MHC proteins confer differential sensitivity to CTLA-4 and PD-1 blockade in untreated metastatic melanoma

Scott J. Rodig[1,2]*, Daniel Gusenleitner[1], Donald G. Jackson[3], Evisa Gjini[1], Anita Giobbie-Hurder[4], Chelsea Jin[3], Han Chang[3], Scott B. Lovitch[2], Christine Horak[3], Jeffrey S. Weber[5], Jason L. Weirather[4], Jedd D. Wolchok[6], Michael A. Postow[6,7], Anna C. Pavlick[5], Jason Chesney[8], F. Stephen Hodi[9]*

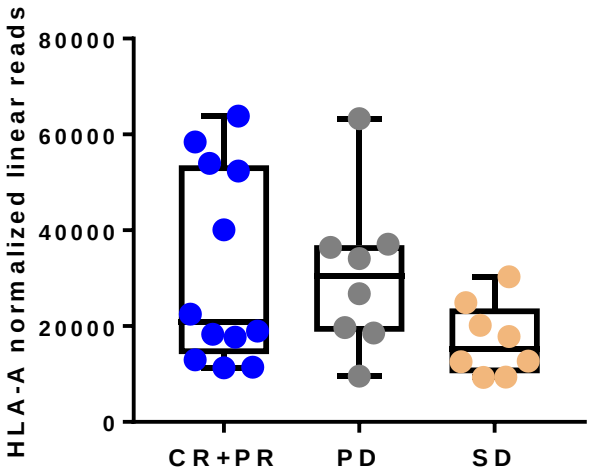
Combination anti–cytotoxic T lymphocyte antigen 4 (CTLA-4) and anti–programmed cell death protein 1 (PD-1) therapy promotes antitumor immunity and provides superior benefit to patients with advanced-stage melanoma compared with either therapy alone. T cell immunity requires recognition of antigens in the context of major histocompatibility complex (MHC) class I and class II proteins by $CD8^+$ and $CD4^+$ T cells, respectively. We examined MHC class I and class II protein expression on tumor cells from previously untreated melanoma patients and correlated the results with transcriptional and genomic analyses and with clinical response to anti–CTLA-4, anti–PD-1, or combination therapy. Most (>50% of cells) or complete loss of melanoma MHC class I membrane expression was observed in 78 of 181 cases (43%), was associated with transcriptional repression of *HLA-A*, *HLA-B*, *HLA-C*, and *B2M*, and predicted primary resistance to anti–CTLA-4, but not anti–PD-1, therapy. Melanoma MHC class II membrane expression on >1% cells was observed in 55 of 181 cases (30%), was associated with interferon-γ (IFN-γ) and IFN-γ–mediated gene signatures, and predicted response to anti–PD-1, but not anti–CTLA-4, therapy. We conclude that primary response to anti–CTLA-4 requires robust melanoma MHC class I expression. In contrast, primary response to anti–PD-1 is associated with preexisting IFN-γ–mediated immune activation that includes tumor-specific MHC class II expression and components of innate immunity when MHC class I is compromised. The benefits of combined checkpoint blockade may be attributable, in part, to distinct requirements for melanoma-specific antigen presentation to initiate antitumor immunity.

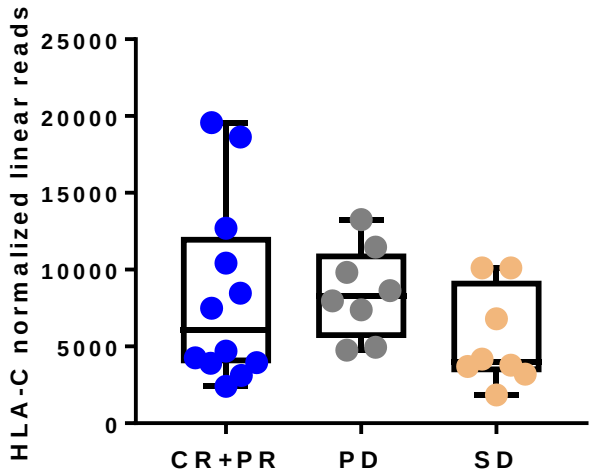


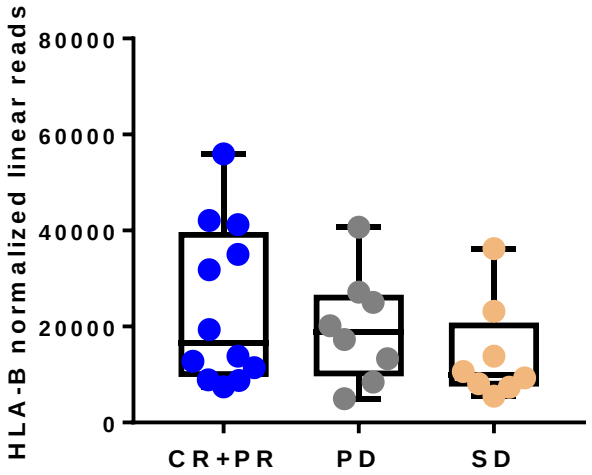
Rodig et al., 2018 *Sci Transl Med*

Does MHC class I expression correlate with response?

MHC class I expression at baseline







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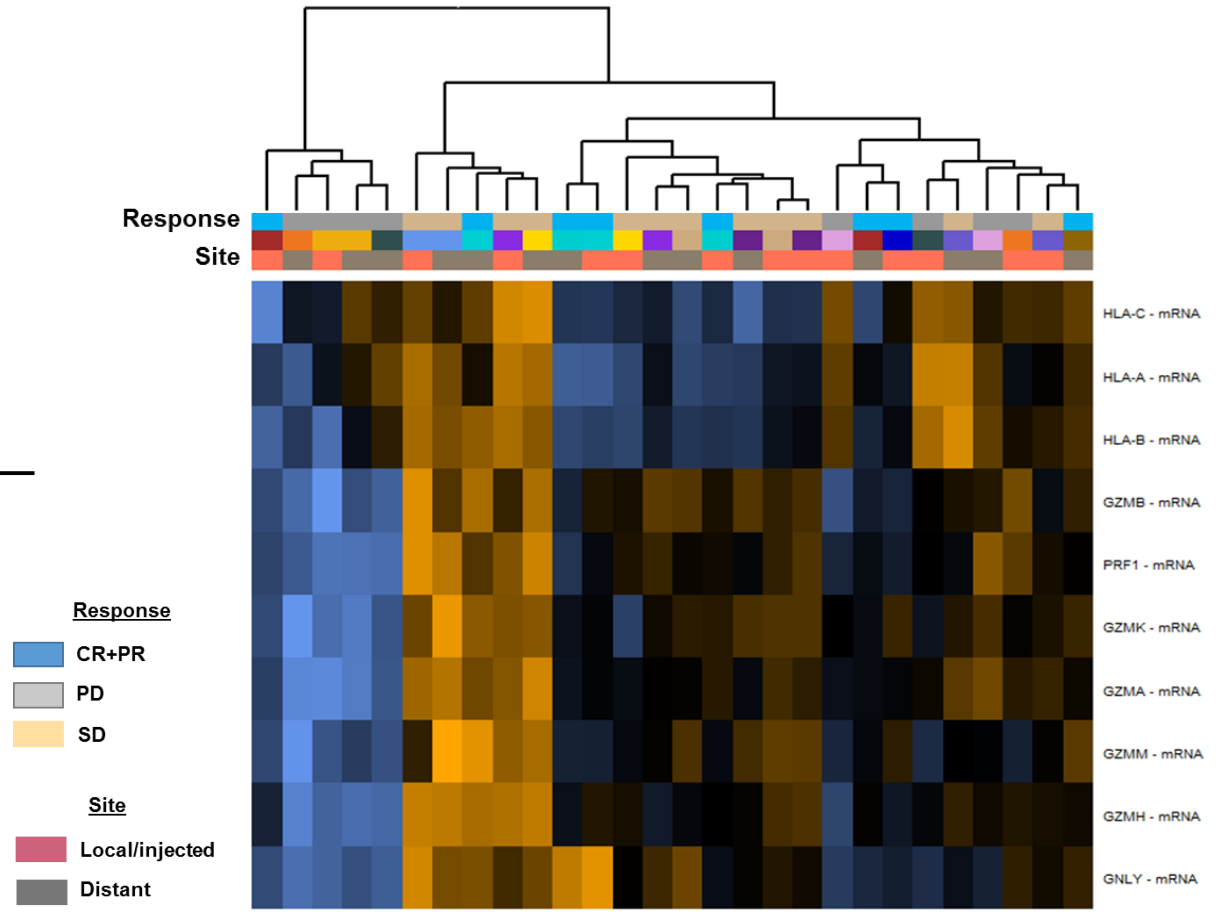
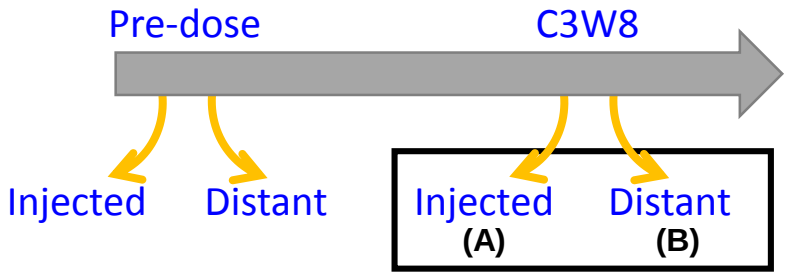
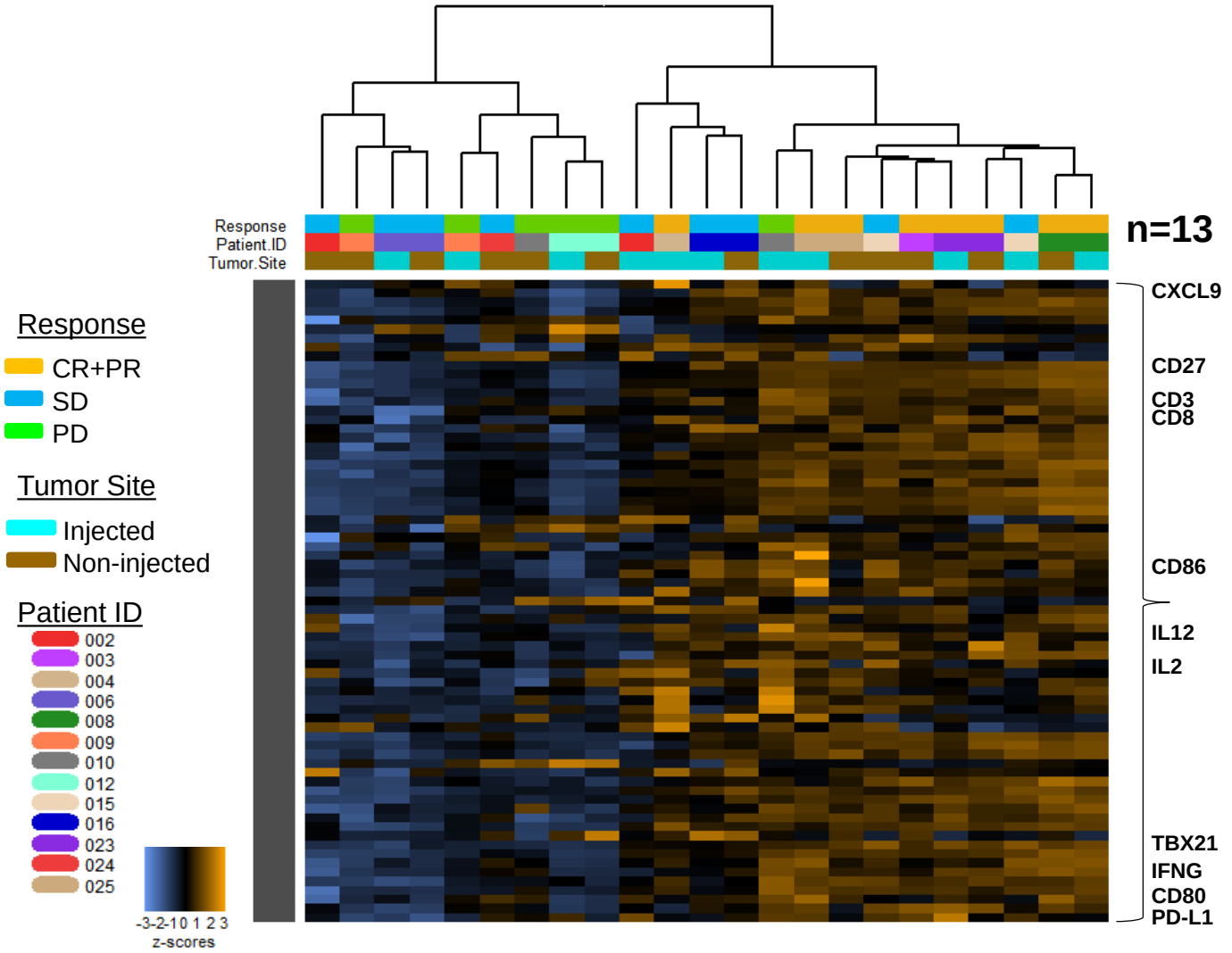


Haymaker….Diab et al., under review

Combination therapy induces CD8+ TIL activation early on-treatment in responding patients

Activation at C3W8 by Nanostring





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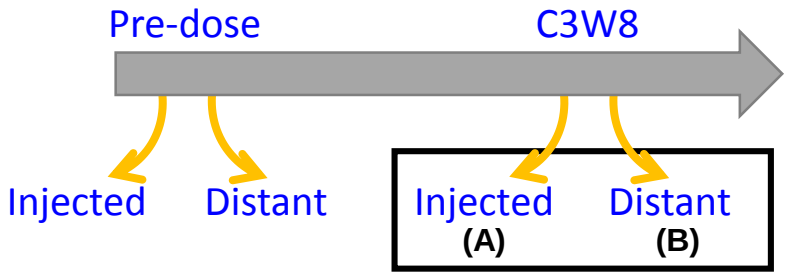
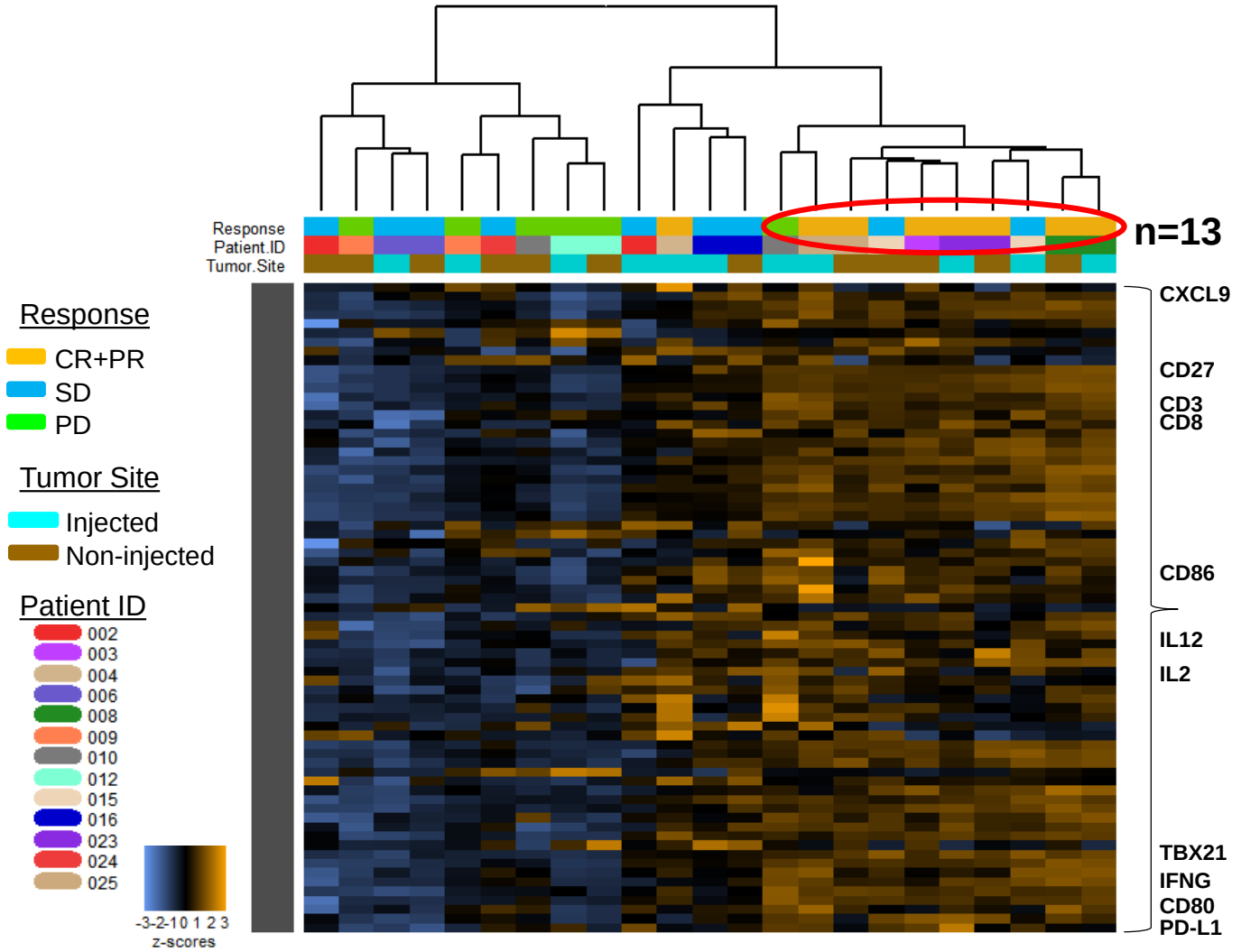
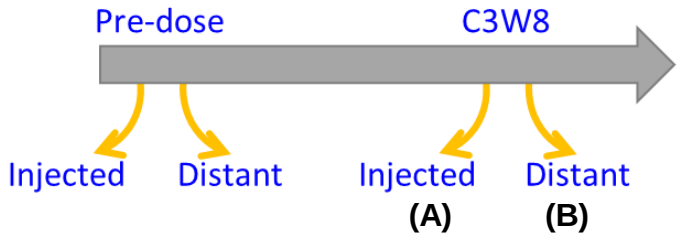
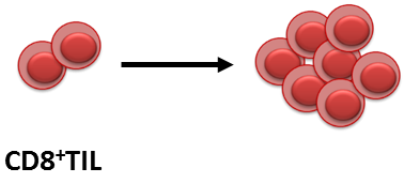




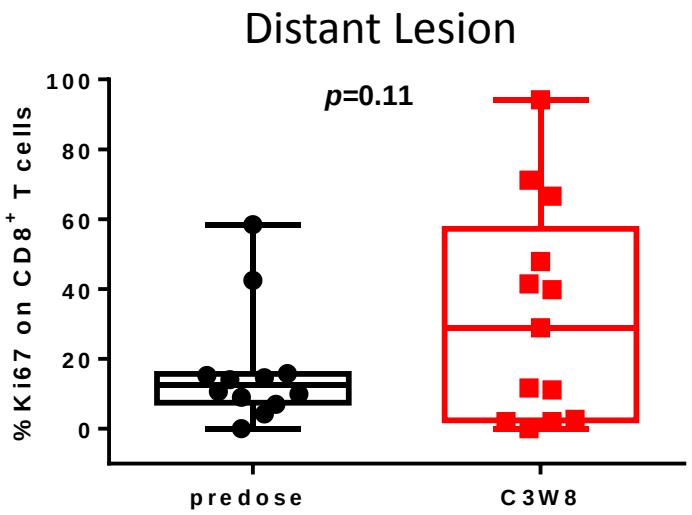
Haymaker….Diab et al., under review

Combination therapy induces CD8+ TIL proliferation and CTL function





Proliferation by flow cytometry



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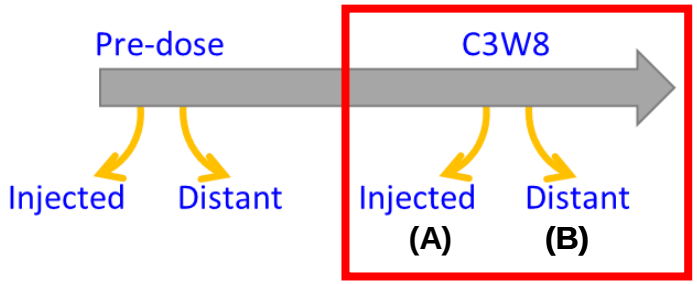
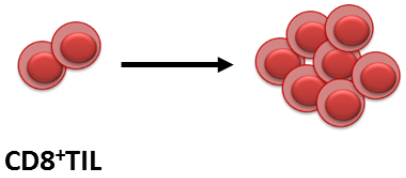
Combination therapy induces CD8+ TIL proliferation and CTL function





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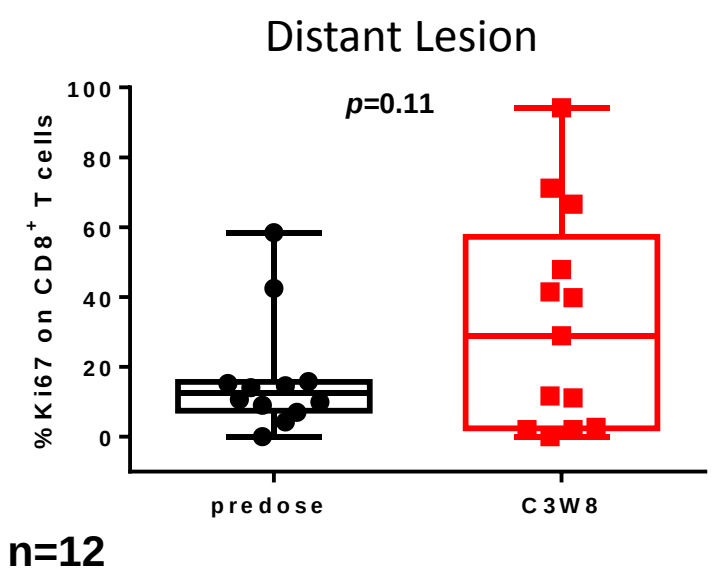

Function at C3W8 by Nanostring

Haymaker et al., under review

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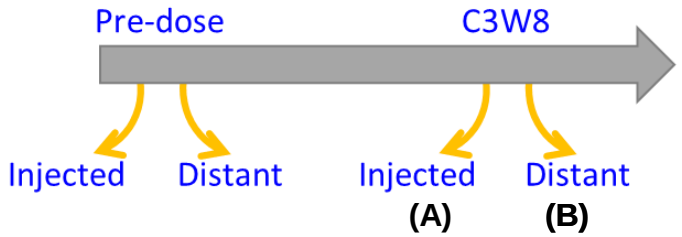

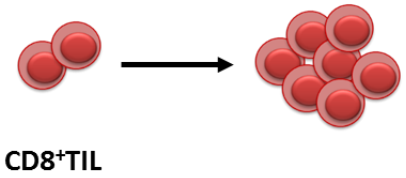

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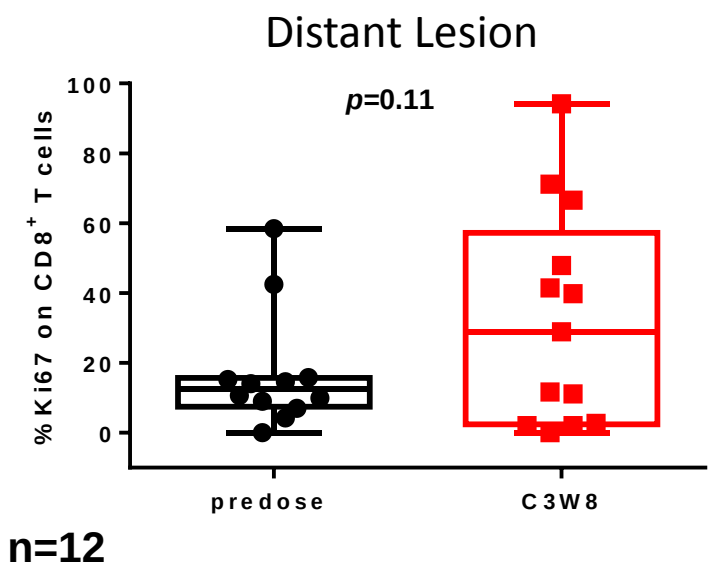

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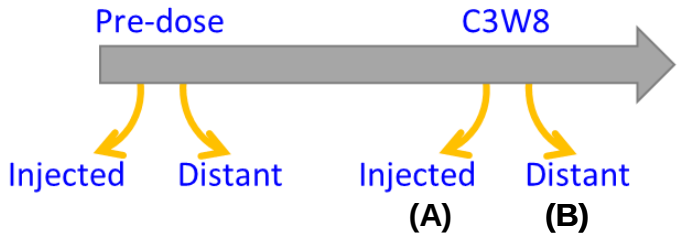

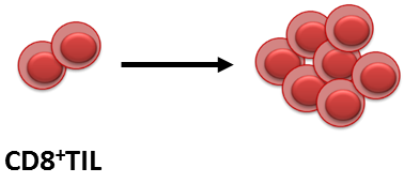

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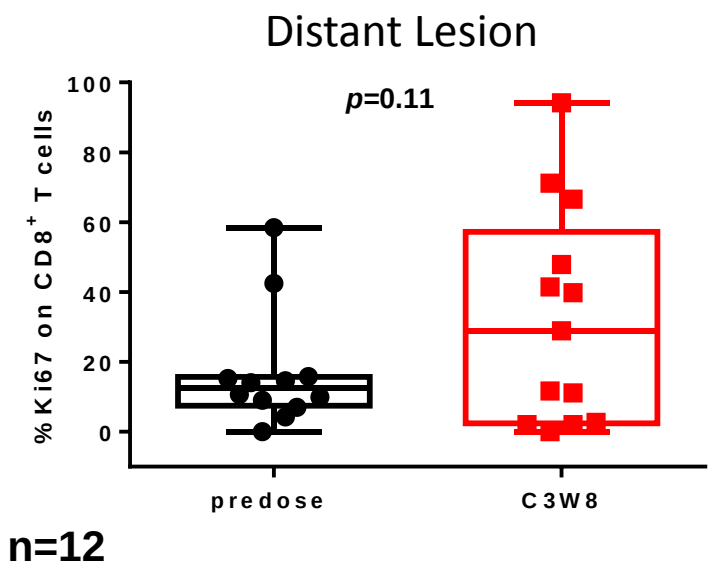

Function at C3W8 by Nanostring

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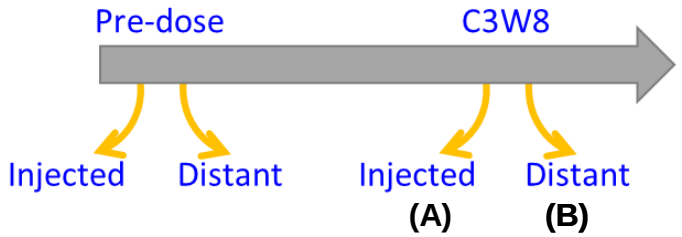

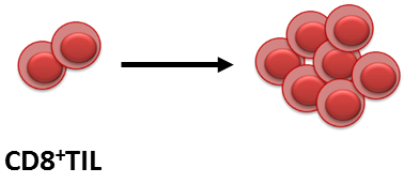

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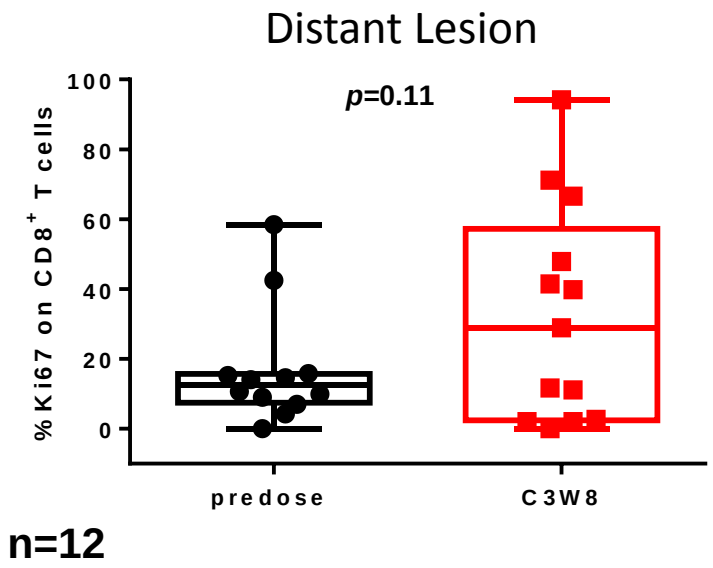
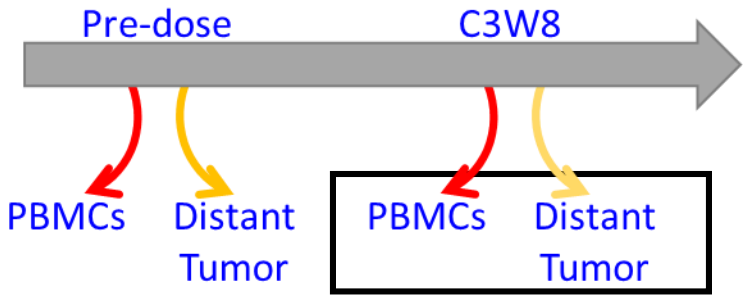
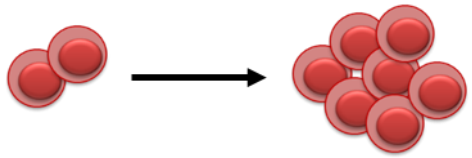


Function at C3W8 by Nanostring

Haymaker….Diab et al., under review

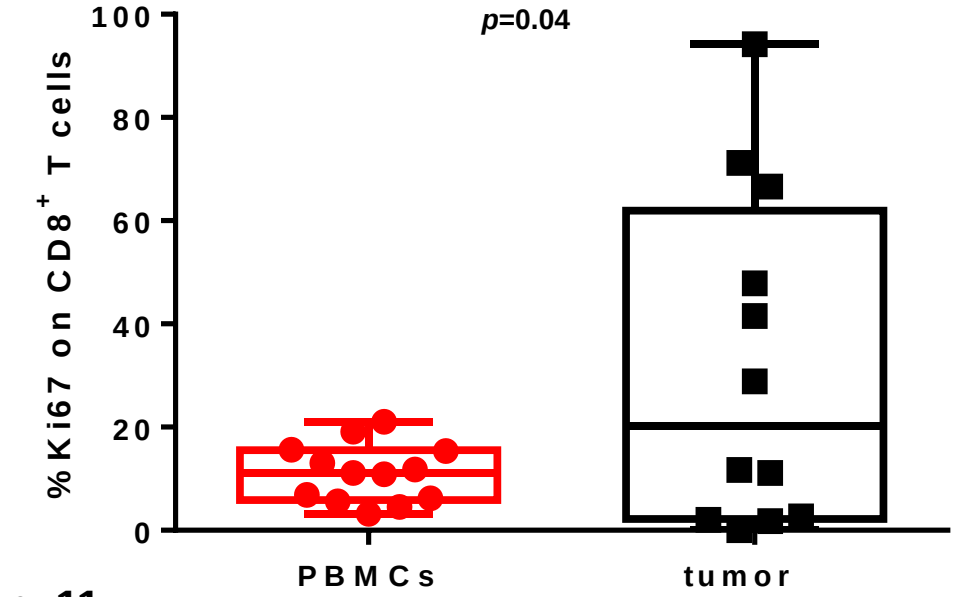
Preferential CD8+ T-cell proliferation at the distant lesion





CD8+TIL

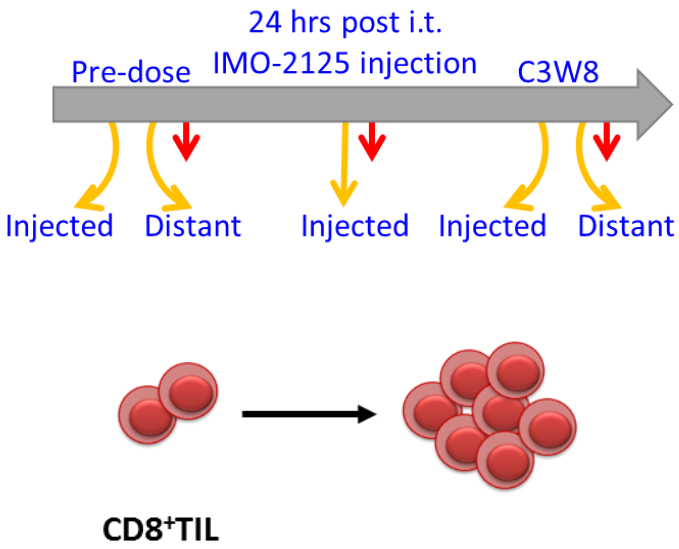
Time point: C3W8

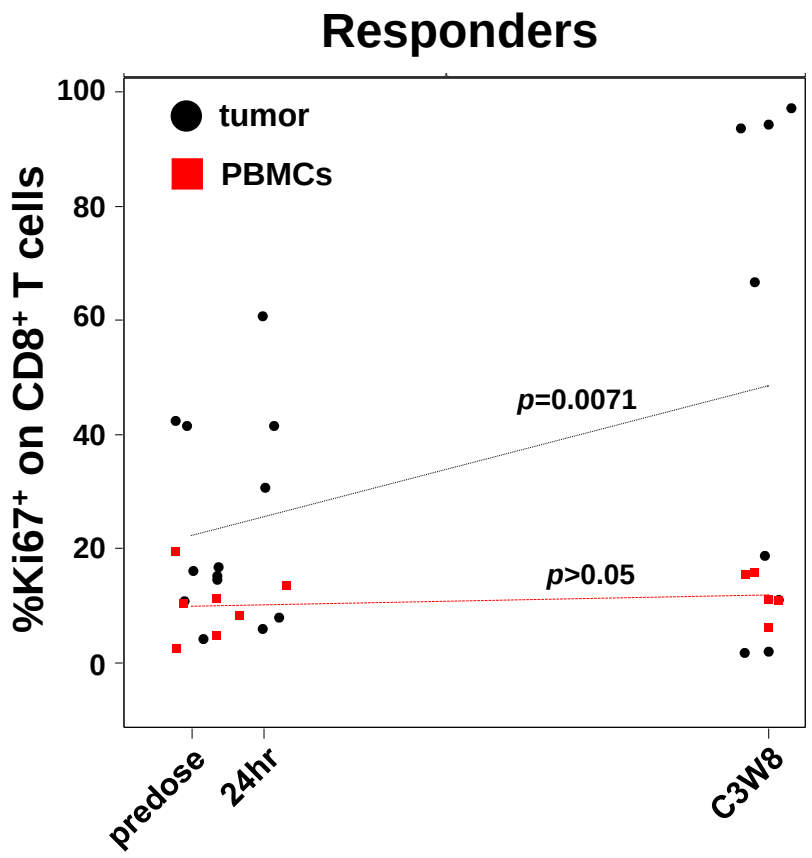


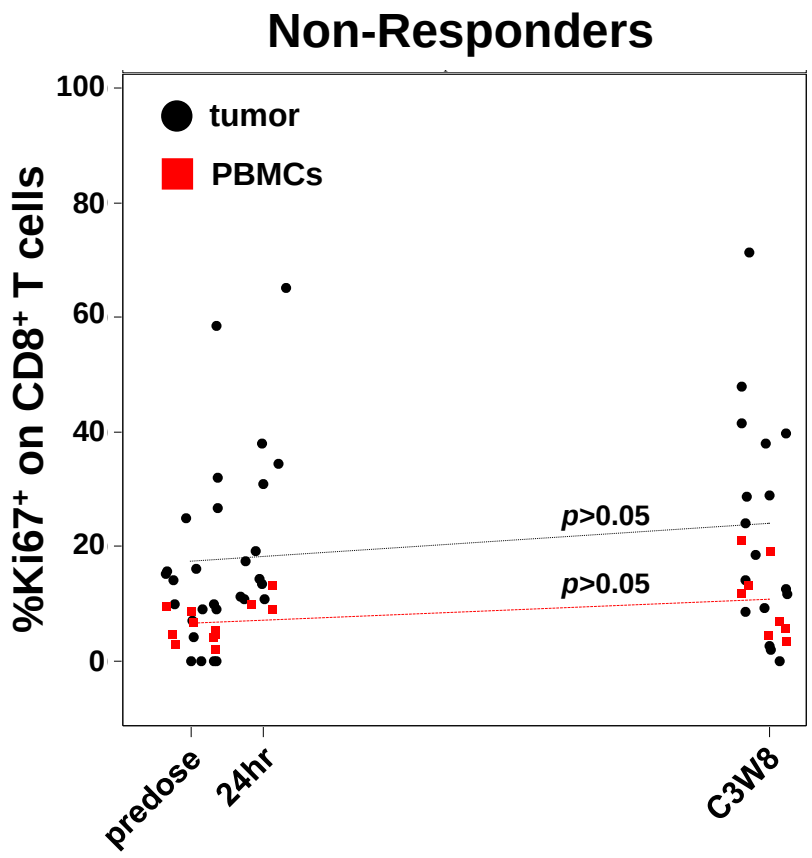
n=11

Haymaker….Diab et al., under review

Selective increase in CD8$^+$ T-cell proliferation in the tumors of responding patients

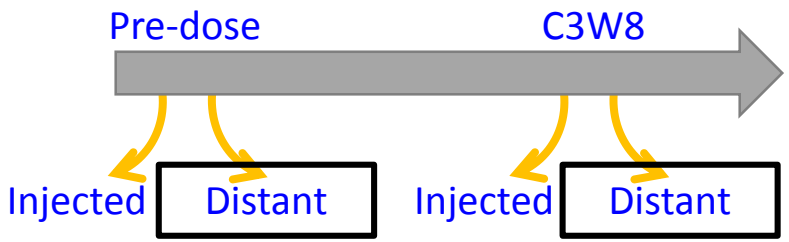


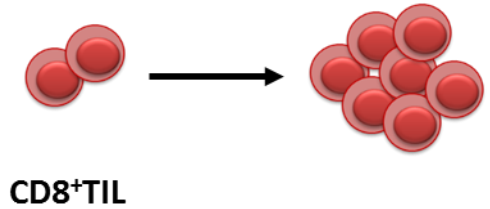


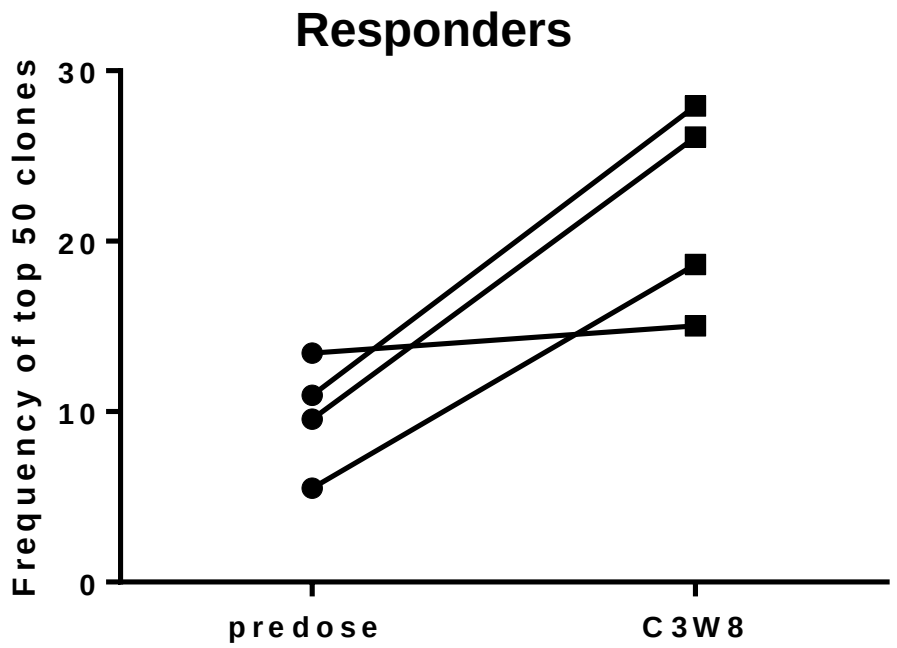


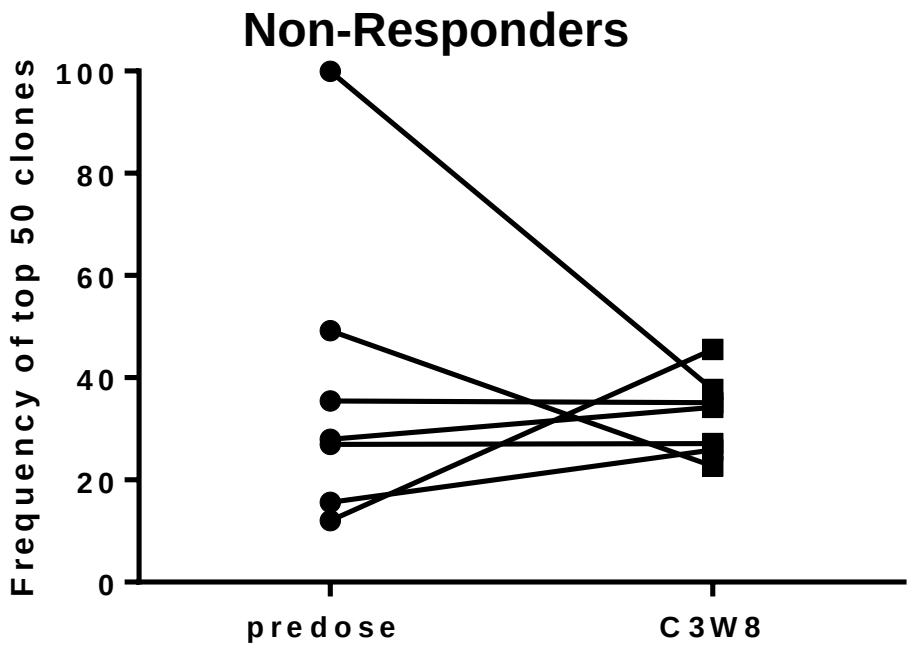
Haymaker….Diab et al., under review

Expansion of top 50 T-cell clones in the distant lesion of responding patients





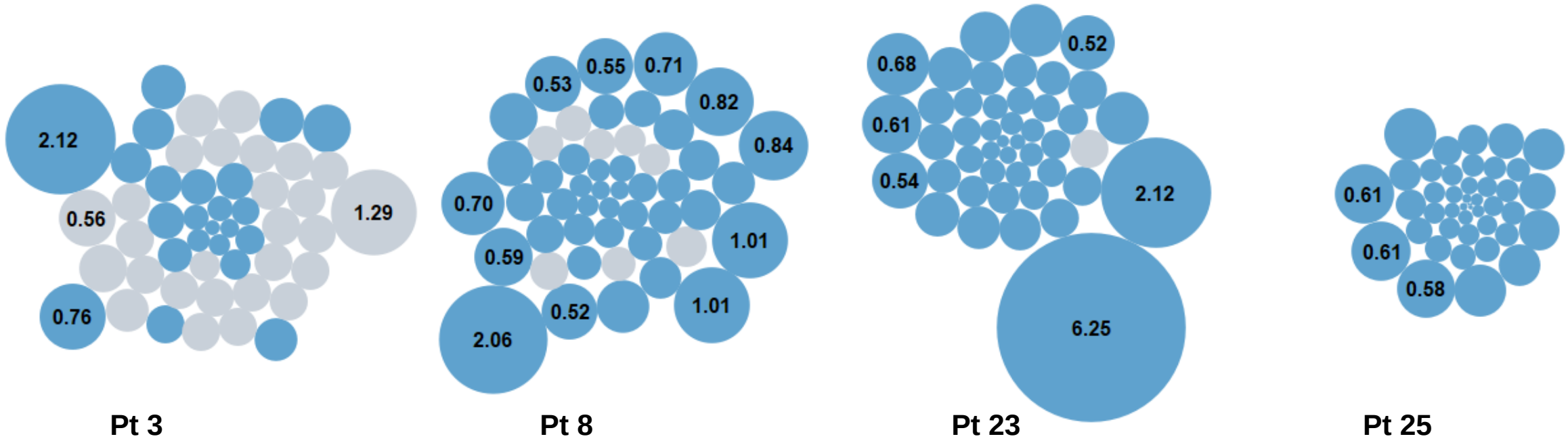




Haymaker….Diab et al., under review

Expanding clones in the distant lesion are shared with the injected lesion

Top 50 clones in the distant lesion at C3W8 of responding patients



Number = clonal specific change in frequency (C3W8 – predose)
Circle size reflects the frequency of the clone relative to the other clones present at C3W8

Haymaker….Diab et al., under review

Conclusion

- Key points
  - –IMO-2125 induces a strong type 1 interferon gene signature, macrophage influx and robust DC maturation post injection independent of ipilimumab
  - –Combination therapy induces $CD8^+$ T cell proliferation and activation that is preferential to the tumor
  - –Major T-cell clones expanding on therapy in responding patients are shared between local and distant lesions indicating that priming/reactivation is to a shared antigen
- Potential impact on the field
  - –Combining intra-tumoral DC activation to enhance T-cell priming with checkpoint blockade may be key in IO refractory patient population
  - –A local tumor can be used as an *in situ* vaccine through activation of local APCs and injection of one lesion results in regression of distant lesions that may not be easily accessible
- Lessons learned
  - –On-treatment biopsy timing is critical!!
  - –Know your cellular target

ILLUMINATE-301 – Trial Design
PD-1 Refractory Metastatic Melanoma

illuminate
Tilsotolimod Clinical Trials

Patient Stratification

– Duration of prior anti-PD-1 therapy (<12 or ≥12 weeks)
– Metastasis stage (M1c or other)
– BRAF mutation status and prior targeted therapy
BRAF wild type, mutation positive with, or without prior targeted

Key Inclusion Criteria:
- Age ≥18 years
- Stage III or Stage IV melanoma
- ≥ 1 measurable lesion accessible for injection
- ECOG PS ≤1
- Adequate organ function

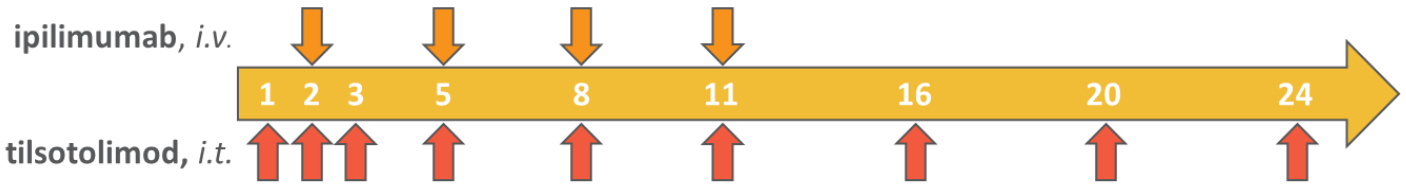
Key Exclusion Criteria:
- Prior TLR agonists
- Prior ipilimumab
- CNS disease

Randomization
1:1
N≈454

Arm A
- Ipilimumab 3 mg/kg (4 doses: weeks 1, 4, 7, and 10)
- Treatment Duration: 10 weeks

No crossover

Arm B
- Ipilimumab 3 mg/kg (4 doses: weeks 2, 5, 8, and 11) +
- Intratumoral tilsotolimod 8 mg (9 doses: weeks 1, 2, 3, 5, 8, 11, 16, 20, and 24)
- Treatment Duration: 24 weeks



Endpoints

Primary endpoint family
– ORR by independent review per RECIST v1.1
– OS

Key secondary endpoints
– Durable response rate
– Time to response
– Progression-free survival
– Patient-reported outcomes
– Safety

i.v., intravenous; i.t., intratumoral; ORR, overall response rate; OS, overall survival,

Acknowledgements

MDACC

Cara Haymaker
Chantale Bernatchez
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Marihella James
Michael Tetzlaff
Patrick Hwu
Willem Overwijk
Salah Bentebibel
Ankit Bhatta
Houssein Safa

MDACC Interventional Radiology Team

Clinical Collaborators

Robert Andtbacka
Douglas Johnson
Montaser Shaheen

Patients and their families

Idera Collaborators

Clayton Fletcher
Joanna Horobin
Sri Chunduru
Shah Rahimian
Jim Geib
Daqing Wang
Robert Doody

Sudhir Agrawal

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Regulation of TLR7/9 responses in plasmacytoid dendritic cells by BST2 and ILT7 receptor interaction

Wei Cao,[1] Laura Bover,[1] Minkwon Cho,[3] Xiaoxia Wen,[2] Shino Hanabuchi,[1] Musheng Bao,[1] David B. Rosen,[4] Yi-Hong Wang,[1] Joanne L. Shaw,[1] Qiumei Du,[1] Chun Li,[2] Naoko Arai,[3] Zhengbin Yao,[5] Lewis L. Lanier,[4] and Yong-Jun Liu[1]

Dose-finding phase : IMO-2125 + Ipilimumab

- 18 subjects treated with IMO-2125 doses from 4 – 32 mg (with standard ipilimumab)
  - Patient population was **refractory to PD-1 inhibitors** and had a high frequency of visceral metastases
  - Patients were injected in a single focus of tumor; deep visceral injections were permitted
- Safety:
  - No DLT, treatment-related deaths or discontinuations from therapy
  - Immune-related AE were similar to ipilimumab monotherapy
  - RP2D selected as IMO-2125 8 mg with standard ipilimumab